A randomized control trial comparing the efficacy of Clonidine premedication versus intraoperative Dexmedetomidine infusion on anaesthetic requirement, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinal fusion

This dissertation is in partial fulfillment of the requirement for the M.D. Degree (branch X) Anaesthesiology examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be conducted in April 2015.

CERTIFICATE

This is to certify that this dissertation **"A randomized control trial comparing the efficacy of oral clonidine premedication with intraoperative Dexmedetomidine infusion on anaesthetic requirement, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinal fusion."** is an original research work done by Dr. George Prashanth Kurian towards partial fulfillment of the requirements for the award of MD Anaesthesiology degree.

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April 07, 2014

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Sub: **Fluid Research grant project:**
A randomized control trial comparing the efficacy of oral clonidine premedication with dexmedetomidine infusion in the perioperative period on sevoflurane requirement and recovery from anaesthesia in patients undergoing two or more than two levels of spinal decompression and instrumented spinal fusion.
Dr. George Prashanth Kurian, Anaesthesiology, Dr. Ramamani Mariappan, Dr. Sajan Philip George, CMC, Vellore.

Ref: IRB Min No: 8577 [INTERVEN] dated 27.11.2013

Dear Dr. George Prashanth Kurian,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A randomized control trial comparing the efficacy of oral clonidine premedication with dexmedetomidine infusion in the perioperative period on sevoflurane requirement and recovery from anaesthesia in patients undergoing two or more than two levels of spinal decompression and instrumented spinal fusion." on November 27th, 2013.

The Committee reviewed the following documents:

1. IRB application format
2. Curriculum Vitae' Drs. George Prashanth Kurian, Ramamani Mariappan, Sajan Philip George.
3. Consent form (English & Tamil)
4. Information sheet (English & Tamil)
5. No of documents 1 -3

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The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on November 27th, 2013at 9.45 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. B. Poonkuzhali	MSC, PhD	Professor, Haematology, CMCH.	Internal, Basic Medical Scientist
Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMCH.	Internal, Clinician
Dr. Molly Jacob	MBBS, MD, PhD	Professor, Biochemistry, CMCH.	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, CMCH.	Internal, Clinician
Dr. Vinod Joseph Abraham	MBBS, MD, MPH	Professor, Community Medicine, CMCH.	Internal, Clinician
Dr. Sukriya Nayak	MBBS, MS	Professor, General Surgery, CMCH	Internal, Clinician
Dr. Deepak Abraham	MBBS, MS	Professor, Endocrine Surgery, CMCH.	Internal, Clinician
Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMCH.	Internal, Basic Medical Scientist
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Hence we approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

The trial need to be registered with Clinical Trial Registry India (CTRI) http://ctri.nic.in before commencing.

The study will need to be submitted to a three monthly data-safety monitoring board (DSMB) review with duly filled in form found in the link http://172.16.11.136/Research/IRB_Polices.html

In case of adverse event, it has to be reported to the IRB Compensation Committee with duly filled in SAE format addressed to Dr. Denise Fleming, Clinical Pharmacology, CMC as a hard copy. The soft copy addressed to saeclinpharm@gmail.com and copy to research@cmcvellore.ac.in.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals entitled: "A randomized control trial comparing the efficacy of oral clonidine premedication with dexmedetomidine infusion in the perioperative period on sevoflurane requirement and recovery from anaesthesia in patients undergoing two or more than two levels of spinal decompression and instrumented spinal fusion." every month along with the

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serious adverse events. Please send copies of this to the Research Office (research@cmcvellore.ac.in) and to Department of Clinical Pharmacology (saeclinpharm@gmail.com) respectively.

Fluid Grant Allocation:

A sum of 80,000/- INR (Rupees Eighty Thousand only) for 2 years. (A sum of Rs 40,000/- will be released for I st installment subsequent installment of 40,000/- each will be released at the end of the first year following the receipt of the interim progress report.)

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

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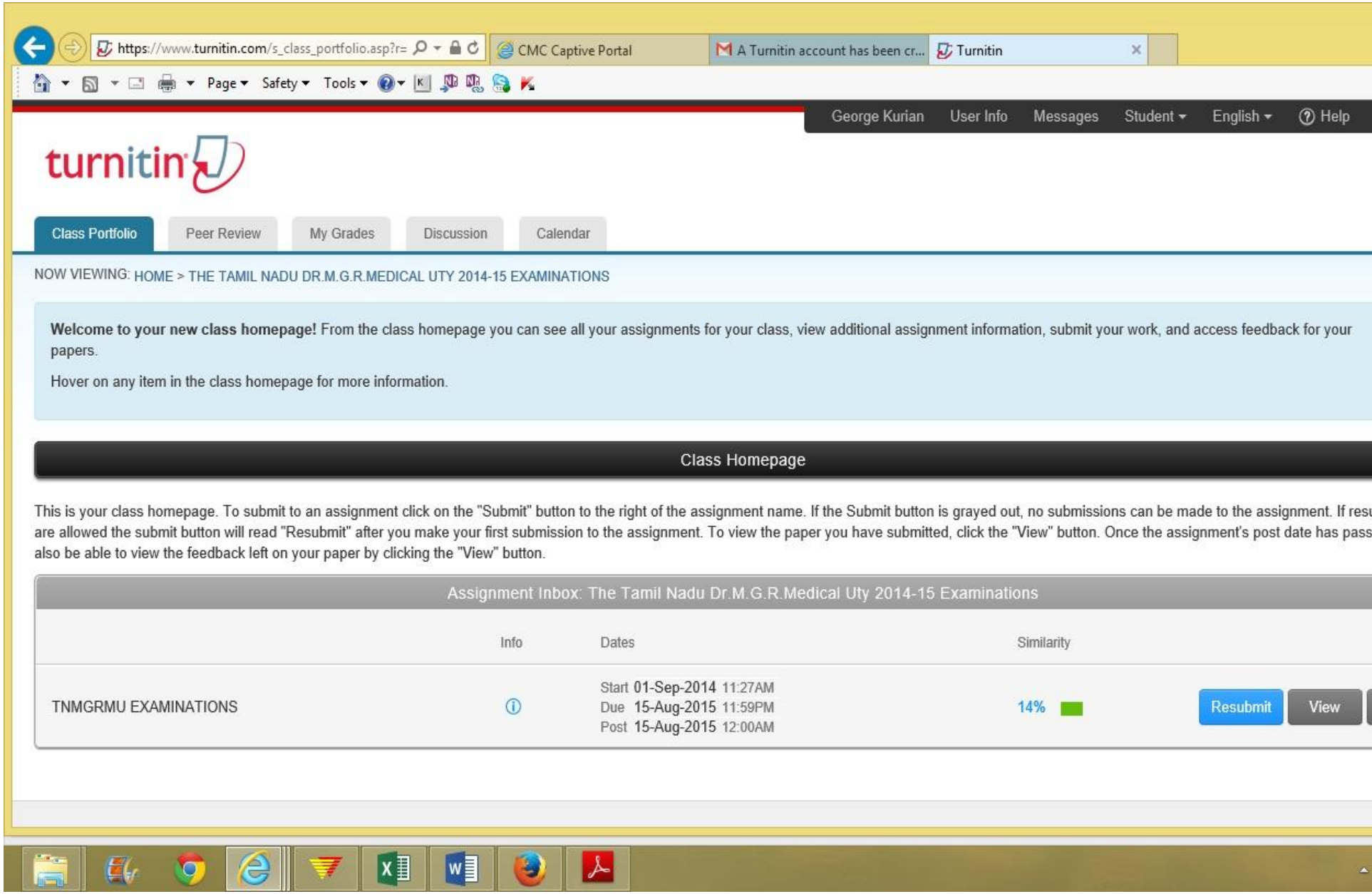
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I would like to thank **Dr Mary Korula**, the Head of the Department, Department of Anaesthesia for allowing me to conduct this study.

I express my heartfelt gratitude to **Dr.Ramamani M**, Associate Professor Department Anaesthesia, Christian Medical College,Vellore for the help and excellent guidance during the study.

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I am greatly indebted to all my patients who agreed to participate with a willing spirit.

Above all I thank the God Almighty for being my strength and guiding me from the beginning to the end of this endeavour.

TABLE OF CONTENT

ABSTRACT

Title of abstract**:** A randomized control trial comparing the efficacy of Clonidine premedication versus intraoperative Dexmedetomidine infusion on anaesthetic requirement, haemodynamics and recovery from anaesthesia in patients undergoing instrumented spinal fusion

Department: Anaesthesia

Name of Candidate: Dr George Prashanth Kurian

Degree and subject: MD Anaesthesiology

Name of Guide: Dr Ramamani Mariappan

Objectives:

To compare the effects of clonidine with dexmedetomidine on sevoflurane requirement, recovery time, haemodynamics further requirement of anaesthetics, incidence of adverse events and amount of blood loss in patients undergoing spine surgery.

Methods:

We conducted a randomized controlled trial comparing oral clonidine premedication and intraoperative dexmedetomidine infusion. Group 1 received oral clonidine in the ward and group 2 received dexmedetomidine infusion intraoperatively. The end tidal concentration of sevofluorane was titrated to keep a BIS score of 40-50. End tidal sevofluorane concentrations and haemodynamic parameters like blood pressure and heart at various time intervals, wake up times, additional propofol and fentanyl requirements and blood loss were recorded.

The mean, standard deviation and frequencies with percentages of these parameters were calculated. The statistical analysis was performed using independent sample t-test. P value < 0.05 was considered statistically significant.

Results:

Both, Clonidine and dexmedetomidine decreases the sevoflurane requirement. But dexmedetomidine has better anesthetic sparing property when compared to clonidine. Intraoperative requirement of propofol and fentanyl were same with both clonidine and dexmedetomidine. Recovery time was comparable between the two groups. Both, clonidine and

dexmedetomidine are effective in controlling haemodynamics including the blood pressure and heart rate. Both, clonidine and dexmedetomidine are equally effective in reducing the blood loss.

Key words:

Clonidine, Dexmedetomidine, anaesthetic requirements, haemodynamic responses.

INTRODUCTION

Patients with spinal problems undergo surgery most often in the prone position. The prone position has been pioneered by spinal surgeons from the 1930s and 1940s onwards because of the need for better surgical access[1]

In addition to the limitations imposed by improper positioning and supports in the prone position which made surgical access difficult and lead to increased bleeding because of increased intra-abdominal pressure, the existing anaesthetic techniques at the time, whereby most patients were left breathing spontaneously and with increased muscle tone also further worsened bleeding and impaired the surgical field even more. Studies have also shown a propensity for significant haemodynamic changes in patients in the prone position[2]. A change in the cardiac index of upto 20% has been noted in patients undergoing surgery in the prone position.[1] This has been attributed to various factors like an increase in intrathoracic pressure and Inferior Vena Caval compression leading to reduced venous return and reduced stroke volumes. Increased intra-abdominal pressures would force blood from the inferior vena cava and into the extradural venous plexuses, leading to increased bleeding and a poorer surgical field.

Administering anaesthesia for a patient undergoing spine surgery has its own set of unique challenges for the anaesthetist especially with respect to fluctuating haemodynamics.. The anaesthetic goals in such a patient would be to anticipate changes in haemodynamics and avoid them as best as possible, attempt to reduce the administration of inhalational anaesthetic agents in surgeries where neurological monitoring is being used so that it is not interfered with, and to provide adequate analgesia both intraoperatively and postoperatively using various analgesics

available to anaesthetists. Adhering to these principles will allow for a quick recovery from anaesthesia which is pain free and hence will allow for early neurological deficit assessment.

Patients having spine surgery can have significant hypertensive responses to noxious stimuli like intubation, incision, manipulations etc which in turn can increase blood loss during the surgery[3]. This hypertensive response will require increasing amounts of opioids and probably a higher concentration of the anaesthetic gas and all of this can interfere with neurophysiological monitoring if it is being used for the surgery. Many of these patients will be suffering from chronic pain and will be on treatment for it with opioids, acetaminophen, NSAIDS etc. Controlling pain in opioid naïve patients is a challenge, they require enormous amount of opioid due to opioid tolerance effect. Opioids supplemented with drugs like ketamine (NMDA receptor antagonist) or Dexmedetomidine (α 2 receptor agonist) will provide effective analgesia without the opioid induced side effects like sedation, respiratory depression and post operative nausea and vomiting. . Suitable selection of combination of agents can be crucial in alleviating pain, stress and anxiety while reducing the incidence of deleterious side effects. Multimodal analgesia will not only avoid the side effects of opioids like drowsiness, post operative nausea and vomiting and respiratory depression but also will enable faster recovery which is very important for an early assessment of neurological function. Hence multimodal analgesia has become very popular in anaesthesia where the opioids are combined with other analgesics like NSAIDS, ketamine, acetaminophen or nerve blocks and local infiltration . Multimodal analgesic techniques have been shown to result in less opioid requirements, less pain scores, less nausea and vomiting, less interference with walking and coughing and deep breathing as compared to use of IV opioids in spine surgery patients[4]. With the introduction of newer drugs like alpha 2 agonists into anaesthetic practice, there has been an increased interest in the use of dexmedetomidine to reduce the anesthetic and opioid requirement,

and to improve the quality of recovery. Dexmedetomidine is a potent and highly selective alpha 2 agonist with sympatholytic, sedative, amnesic and analgesic properties which has been noted to be an effective and safe adjunct in several clinical applications. It gives a unique conscious sedation (patients appear to be asleep but are easily arousable), analgesia without respiratory depression. It has a wide safety margin, excellent sedative property and exhibits moderate analgesia. It is the most recently investigated and commercialized drug among alpha 2 agonists.

Clonidine, an α 2 receptor agonist, it has been in anesthesia practice for several decades. There are studies comparing the clonidine with placebo or dexmedetomidine with placebo on anesthetic, analgesic requirement, recovery from anesthesia. Studies comparing the effects of both clonidine and dexmedetomidine during surgery were lacking and hence we have conducted a randomized control trial to compare Tablet clonidine as a premedication versus an infusion of dexmedetomidine given preoperatively and continued intraoperatively and how they affect requirements of inhalational agents, haemodynamic responses intraoperatively and time taken by the patient to wake up from anaesthesia. In addition we have compared the incidence of adverse events like bradycardia and hypotension between the two groups and also the blood loss between the two groups.

AIMS

Aim of the study:

To compare the effects of clonidine premedication with intra operative infusion of Dexmedetomidine on anesthetic and analgesic requirement and recovery from anaesthesia, in patients undergoing instrumented spinal fusion.

OBJECTIVES

Objective of the study:

1. To compare the effects of oral clonidine premedication with intraoperative infusion of intravenous dexmedetomidine on sevoflurane requirement and the recovery time in patients undergoing major spine surgery and fusion.

2. To compare the haemodynamic responses to intubation and during surgery.

3. To compare the further requirement propofol and fentanyl intraoperatively during surgery.

4. To compare the incidence of adverse events like hypotension, bradycardia and hypertension between the two groups.

5. To compare the blood loss during surgery in both groups.

REVIEW OF LITERATURE

Review of literature

Spine Surgery and anaesthetic implications

As an anaesthesiologist caring for patients undergoing spine surgery, one must be aware of the various anaesthetic concerns related to such a position and also to the nature of the surgery. Aspects of anaesthetic management for spine surgery can include management of the airway, management of significant haemodynamic changes,[5] caution while positioning the patient to avoid complications like nerve injury, blood vessel compression, injury to the eyes, anaesthetic techniques to minimize blood loss,[6]anaesthetic techniques to reduce the inhalational agent requirement so that it does not interfere with neurophysiological monitoring readings, and finally to provide good post operative pain relief. Emphasis must be given to ensure a good surgical field by reducing the bleeding and ensuring the patient awakes rapidly and is able to respond to commands to assess neurological function.

Spine surgery can be extremely painful and the noxious stimuli of surgical incision can evoke an exaggerated stress response with attendant tachycardia and hypertension. In such a situation, for adequate anaesthesia, the patients will require a much higher dose of the anaesthetic agent. Such a high level of inhalational agent being administered to the patient will not only interfere with neurophysiological monitoring, but it will also delay awakening and neurological assessment[7]. Also, to ensure adequate analgesia, one will have to administer higher doses of

opioids and contend with all the side effects of opioids like respiratory depression and post operative nausea and vomiting and tolerance.

This is where alpha 2 agonists like clonidine and dexmedetomidine come into play in anaesthesia. These drugs are known to act on central alpha 2 receptors, provide sedation and anxiolysis and hence reduce anaesthetic and analgesic requirements. Clonidine is even used in conjunction with regional anaesthesia to prolong duration of block. Owing to these properties, if one were to use either clonidine or dexmedetomidine as an anaesthetic adjunct, one would be able to reduce the dose of the inhalational agent being used and hence not interfere with neurophysiological monitoring and also be able to reduce the opioid requirement and negate the side effects of excessive opioids.

Use of alpha 2 agonists in the anaesthetists armamentarium has been in vogue since the 1970's, either as an anaesthetic adjunct intraoperatively or even as premedication. Clonidine was the drug that was classically being used for this purpose.[89]. This was largely due to its anxiolytic, sedative and analgesic properties. Recently however, Dexmedetomidine, a newer drug belonging to the same class of drugs has come to the fore and has gained a lot of popularity among anaesthetists. It is gaining more and more acceptance in both anaesthetic practice and in the ICU set up as more and more studies are being conducted on it. This is attributable to the fact that it has more selective alpha 2 agonist action than clonidine ie its affinity is 8 times more than clonidine's towards alpha 2 receptors[10].

Spine surgery is very often associated with considerable amounts of blood loss leading to hypotension, which can compound problems of nerve injury, injury to the eye and spinal cord function. Hence blood loss and hypotension are both undesirable in the spine patient undergoing

surgery in the prone position. Different factors that are postulated to play a role in increasing volume of blood loss are surgical technique and expertise, anaesthetic techniques, number of levels being instrumented, duration of surgery, blood pressure and presence of coagulopathies or platelet abnormalities.

Increased blood loss during surgery is associated with increasing amounts of blood transfusions. Blood transfusions are not without their own side effects. Side effects of blood transfusions include:

1) Immediate adverse effects of blood transfusion:

a) Febrile reactions

b) Urticarial reactions

c) Severe allergic reactions

d) Acute hemolytic reactions

e) Bacterial contamination

f) Transfusion related acute lung injury

g) Volume overload

h) Hypothermia

i) Citrate toxicity

j) Hyperkalemia

2) Delayed and long term adverse effects of blood transfusion

a) Delayed hemolysis

b) Alloimmunisation

c) Transfusion associated graft versus host disease

d) Immunomodulatory effects

e) Iron overload

f) Infectious disease transmission

Multiple blood sparing techniques can be employed during spine surgery. They can be classified into:

1)Techniques to reduce the bleeding itself:

a) Controlled hypotension

b) Use of local vasoconstrictors

c) Epidural blockade

d) Chemical or biological agents like aprotinin, epsilon amino caproic acid, tranexamic acid, bone wax etc

2) Techniques that reduce the need for homologous transfusion

a) Acute normovolumic hemodilution

b) Autologous transfusion

c) Cell saving systems

d) Erythropoietin

Out of these, using drugs belonging to the class of alpha 2 agonists, it is possible to induce controlled hypotension in a patient undergoing spine surgery to reduce the blood loss.

Controlled hypotension

Controlled hypotension has been in use now for more than 50 years to reduce blood loss, reduce the need for blood transfusions and its attendant side effects and also to help in providing a satisfactorily bloodless field for surgery to proceed. It was first introduced in 1917 to provide a bloodless field during neurosurgery. Since then many methods like using high spinal, high epidural, ganglion blockade using pentamethonium and hexamethonium, arteriotomy, deep anaesthesia using increased doses of inhalational agents, sodium nitroprusside, beta blockers, calcium channel blockers etc have been used. Nowdays, even alpha 2 agonist drugs like clonidine and dexmedetomidine are being applied in this regard.

In certain surgeries like middle ear surgeries and spine surgeries, even if the amount of bleeding does not appear excessive it can significantly interfere with visualization of the operative field and adversely affect successful outcome of the surgery. A better surgical field helps to improve the surgical technique and dissection and reduces the amount of electrocautery being used. This could potentially have added benefits like less post operative pain and less risk of sepsis.

Controlled hypotension is defined as :

a) A fall in systolic BP to 80-90 **Or**

b) A fall in Mean Arterial BP to 50-65 **Or**

c) A 30% reduction in baseline Mean Arterial BP

The level of hypotensive anaesthesia should be provided till the desired target is achieved, for example a bloodless field, and should be within safe limits of cranial and cerebral blood flow. For example, a patient with chronic hypertension may not be able to tolerate more than a 25% drop in his mean arterial pressure. Similarly, a patient with cerebrovascular disease may not be able to tolerate such a drop in his Blood Pressure.

When inducing controlled hypotension in patients , one must have an understanding of how blood flow to the vital organs is regulated. Even in the setting of controlled hypotension, however, organ damage is rarely expected because blood flow to the organs is well maintained. This is because these vital organs have in place a mechanism called autoregulation. Autoregulation mechanisms include:

1)Stretch myogenic mechanism: Smooth muscles found in the blood vessels respond to altered blood pressure.

2)Passive mechanical: Expansion of encapsulated organs leads to compression of thin walled vessels and hence increases the vascular resistance

3)Metabolic: Production of vasoactive substances increases the blood flow to these organs

As a result of autoregulation the cerebral blood flow is maintained between a range of 45-50ml/100gm/min as long as the MAP is kept between 50-150 mm of Hg. Coronary blood flow is

maintained as long as the MAP is kept between 60-160 mm of Hg. Renal blood flow is kept even between a MAP range of 80-180 mm of Hg.

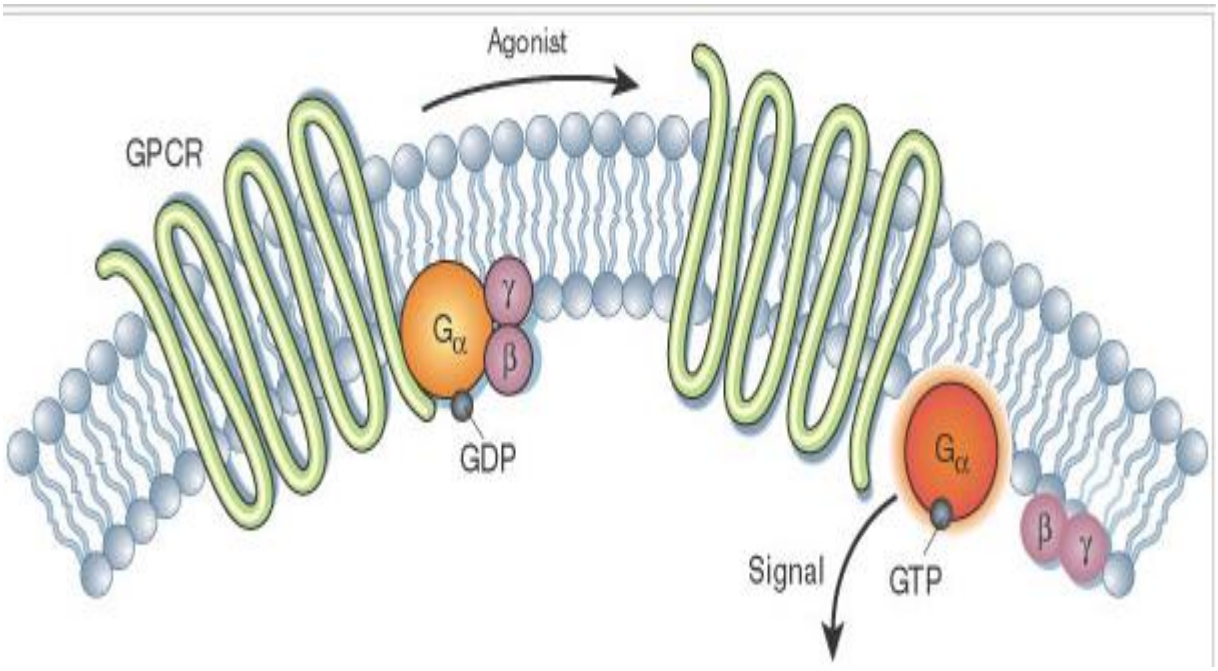
Drugs that are used for controlled hypotension can either be used alone, or in conjunction with other anaesthetic agents as an adjunct and hence can be used to reduce the dose requirements of the other drugs and their potential side effects. Such drugs are many but to be an ideal drug for hypotensive anaesthesia, it must be easy to administer, it must act quickly, it should have an effect that will wear off soon after the surgery, should be eliminated without toxic metabolites and have a predictable dose dependant effect while maintaining adequate perfusion for the vital organs.

Agents that can be used alone successfully include inhalationalanaesthetics, hypotensive agents like sodium nitroprusside and nitroglycerin, remifentanil etc. Drugs that are usually used in conjunction with other anaesthetics are Calcium channel blockers, Beta blockers and Alpha-2 adrenergic agonists. Clonidine and dexmedetomidine have been used as oral premedication and intravenous infusion during anesthesia to induce controlled hypotension.

Alpha 2 agonists

Physiology of adrenoceptors:

All Adrenergic receptors are similar in structure and belong to a class of G protein coupled receptors,that are targeted by catecholamines, especially norepinephrine and epinephrine. G protein coupled receptors sense molecules outside the cell, activate signal transduction pathways inside the cell and ultimately bring about cellular responses. Many cells of the body possess these receptors and generally whenever a catecholamine comes and binds to these receptors, it stimulates sympathetic nervous system activity.



G protein coupled receptor

Dr Raymond Ahlquist, Professor of Pharmacology, in Georgia, USA, published a paper concerning adrenergic nervous transmission in 1948, but its significance was largely ignored. However by 1954, he was able to establish that adrenergic receptors played an important role in the adrenaline and noradrenaline cellular mechanism. This discovery would revolutionize pharmacotherapeutic research, allowing scientists to selectively design specific molecules for therapeutic purposes.

Dr Ahlquist was able to classify these receptors into alpha and beta type of receptors based on responses of various amines in physiological solutions[11].Later he was able to further classify them based on synaptic location. Alpha receptors are further classified into α1 and α2 receptors. α1 receptors are further classified into α 1a, α 1b and α 1d. Similarly α2 receptors are also further classified into α2a, α2b and α2c, which are presynaptic, post synaptic and extrasynaptic. Beta receptors are classified into ß1, ß2 and ß3 types. All of these are linked to G proteins.

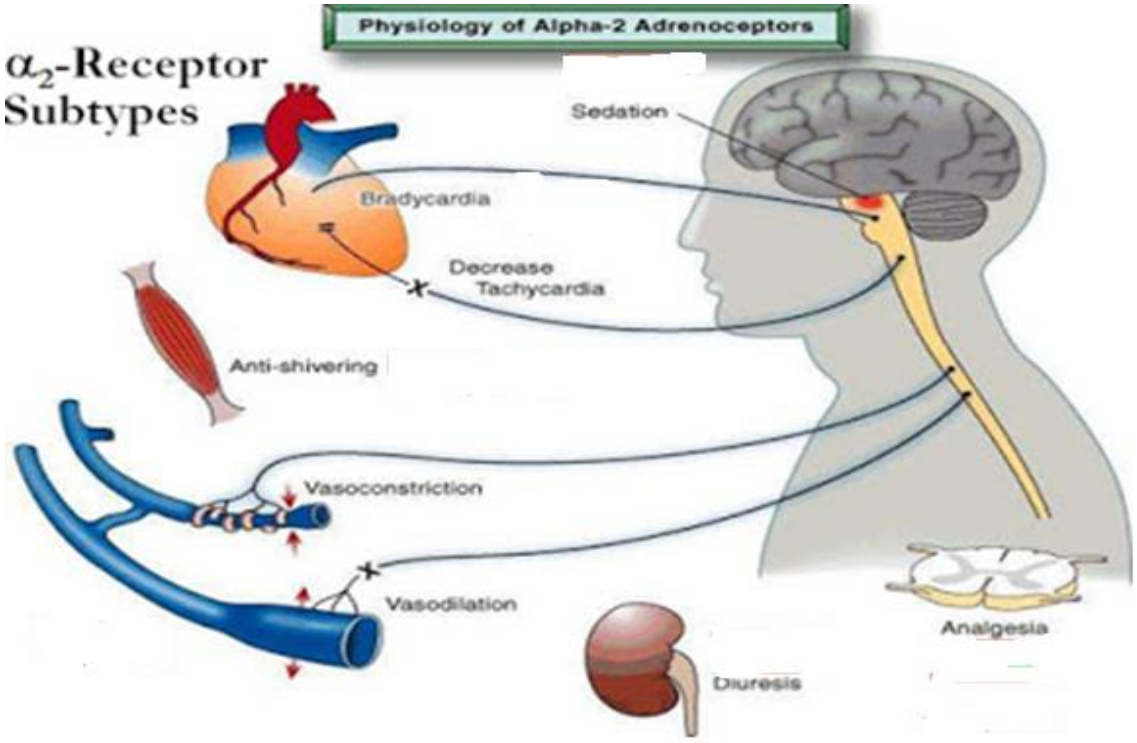
α1 receptors are post synaptic receptors located in the smooth muscles of the eyes, lungs, blood vessels, uterus and gut. α2 receptors are usually found on presynaptic nerve terminals. ß1 receptors are found post synaptically in the heart while ß2 receptors are found largely postsynaptically in the smooth muscles and gland cells. ß3 receptors are found in the gall bladder and brain adipose tissue.

Functionally even though α 1 receptors are always excitatory, it has been found that α 2 receptors can be either inhibitory or excitatory.

Location of α 2 adrenoceptors

There is a high number of alpha 2 receptors in the medullary dorsal motor complex of the brain. Activation of this set of alpha 2 receptors is responsible for the characteristic haemodynamic response of alpha 2 activation. Also, the locus ceruleus has a large number of alpha 2 agonists that are responsible for the sedation and hypnosis actions of alpha 2 agonists. Other sites with high density of alpha 2 receptors are the vagus nerve, the substantiagelatinosa and dorsal horn of the spinal cord [12]

Physiology of alpha 2 receptors.



Clinical implications of alpha 2 actions on different systems

Respiratory System

Unlike most other anaesthetic agents of use to us, Alpha 2 agonists are not known to depress respiration. Also they do not potentiate the action of opioids on depression of respiration. Infact Alpha 2 agonists are commonly chosen as sedation for patients who are difficult to wean from ventilators.

Cardiovascular system

Alpha 2 receptors are found in the peripheral blood vessels. Activation of postsynaptic alpha 2 receptors produces vasoconstriction. Activation of presynaptic alpha 2 receptors prevent release of norepinephrine and hence lead to vasodilation and reduction in heart rate. But protective reflexes that are needed in times of hypotension in the presence of alpha 2 agonist drugs are kept intact because they do not interfere with the release of catecholamine and don't block adrenergic receptors[13].

Central nervous system

In the brain principal site of action of alpha 2 agonists is at the locus ceruleus where they reduce the rate of neuronal firing leading to hypnosis and sedation. Activation of alpha 2 receptors at the dorsal motor nucleus of the medulla leads to a fall in heart rate and blood pressure and activationof these receptors at the intermediolateral cellcolumn and substantiagelatinosa of the spinal cord inhibitsrpractice.eleaseof the substance P and this is responsible for its analgesic effect[14].

Other physiological effects of alpha 2 agonists

1) They can cause diuresis by both inhibiting ADH release and antagonizing the effects of ADH in renal tubules
2) Decongestant and antisialogogue effects
3) Anti- shivering effects.

The introduction of alpha 2 adrenoceptor agonists into anaesthesia is not a new concept. Veterinarians were known to use xylazine and detomidine for a long period to induce analgesia and sedation in animals undergoing preocedures and much of the current knowledge was obtained from this practice.

As a result of their analgesic and sedative effects, Alpha 2 agonists have found their way into clinical use in anaesthetia. Two commonly used such drugs are clonidine and dexmedetomidine. It has recently become evident that complete anaesthesia is possible using potent alpha 2

adrenoceptor agonists like dexmedetomidine as a single agent at a dose of 1-5 mcg/kg/hr during period of 10-15 minutes initially followed by a dose of 0.25 to 1 mcg/kg/hr[15,16].

Clonidine

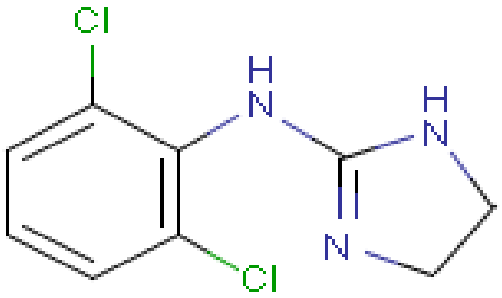
Clonidine Hydrochloride is a centrally acting alpha 2 agonist with hypotensive and sedative and anxiolytic and analgesic effects. It was initially synthesized by deriving it from two known drugs in the 1960s called naphazoline and tolazoline which were alpha sympathomimetic drugs in use at the time. It was originally intended to be used a nasal vasoconstrictor, but during clinical trials of the drug, it was found to bring about hypotension, bradycardia and sedation. As a result, it was introduced in 1966 as an antihypertensive, the first known antihypertensive to act on the CNS.In 1978 it has been used for neuroleptanalgesia [17]. Since then it has also been licensed for the use in treatment of migraines and menopausal flushing[18]. It is also an analgesic, sedative and an anxiolytic. All these characteristics along with its capability of providing haemodynamic stability render clonidine a versatile drug for the anaesthesiologist and intensivist.

Pharmacology:

Clonidine Hydrochloride is an imidazoline derivative and exists as a mesomeric compound. It is an alpha adrenoreceptor agonist which has been in use for the last 40 years and has been extensively investigated with an alpha 2 : alpha 1 ratio of 200:1.

Chemical formula is 2[(2, 6 Dichloro phenyl) Imino] Imidazoline Mono hydrochloride.

Chemical structure:



Clonidine

Mechanism of action:

The action of clonidine is by stimulating the presynaptic alpha 2 adrenoreceptors, leading to reduction in noradrenaline release from both central and peripheral sympathetic nerve terminals[19]. Clonidine brings about its effects by acting at spinal and supraspinal sites including depression of thalamic transmission of impulses to the cerebral cortex and enhancement of descending inhibitory pathways to the dorsal horn.(21) Supraspinally, the locus coeruleus located in the floor of the fourth ventricle is the principle site for the sedative and analgesic action. Noradrenaline concentrationsin the locus coeruleus is significantly lowered by clonidine. The efferents from the locus coeruleus has its actions on the the descending fibres of the reticulospinal tracts tht inhibit transmission of pain at the spinal level [20]. Alpha 2 receptors are concentrated on the dorsal nucleus of vagus which is responsible for the bradycardic and hypotensive effects. They are also found post synaptically on the dorsal horn neurons of the spinal cord and acts by inhibiting the release of

substance P [21]. The analgesic effect of clonidine is by its action on the cholinergic, purinergic and serotonergic pain systems[22]. Various clinical and experimental investigations have documented that alpha 2 agonists administered along with opioids into the spinal cord act synergistically to reduce pain (24).

Pharmacokinetics of clonidine

Clonidine is very rapidly and completely absorbed from the gastrointestinal tract after oral intake. The bioavailability of clonidine is 100%. The high lipid solubility of the drug enables it to easily penetrate the Central Nervous System. Protein binding in the plasma is about 20% with a volume distribution of 1.7-2.5 litre/kg.

Clonidine undergoes metabolism mainly in the liver to inactive metabolites like P-hydroxy clonidine which furthermore undergoes glucuronidation to give O-glucuronide.and 65% of the dose administered is eliminated unchanged in the urine, 20% is excreted in the faeces.95% excretion can be expected within 72 hours from the urine and faeces. Complete elimination can be expected in 5 days time.

The clearance is 1.9 to 4.3 ml/kg/minute[23]. When taken orally, onset of action can be expected from 30-60 minutes and the drug will reach its peak plasma concentration by about 90 minutes. When given intravenously , the peak action occurs in ten minutes and lasts for three to seven hours(24). Its elimination half life can be anywhere between 6-24 hours with a mean of 12 hours. The half life is significantly increased in the presence of renal impairment, hence warranting a reduction in the dose [24].

Pharmacodynamics:

Central Nervous System:

Clonidine produces dose related sedation, analgesia, anxiolysis and a decrease in the requirements of other anaesthetic agents and opioids(24). Clonidine also produces a reduction in cerebral blood flow, cerebral metabolic rate of oxygen consumption and intra ocular pressure(22) . It also has a depressant action on both spontaneous sympathetic outflow and afferent Aδ And C fibre mediated somato sympathetic reflexes [25].

Cardiorespiratory Systems:

An initial transient increase in blood pressure and systemic vascular resistance and a reduction in cardiac output is caused by clonidine due to the activation of post synaptic alpha 2 receptors on the peripheral vasculature. This is followed by a longer lasting reduction in heart rate and blood pressure which is caused by a centrally mediated reduction in sympathetic tone and increased vagal activity(22). Clonidine has no action on cardiac contractility and so cardiac output is well maintained. It can also lead to a reduction in coronary and systemic vascular resistance(27). Protection against myocardial ischemia and improved outcomes in patients who are at risk of cardiac events has been demonstrated for clonidine.

Respiratory depressant action of clonidine is very minimal although it exerts good sedation. No change in respiratory rate, $PaCO_2$, SpO_2 has been observed on administering clonidine(26).

Renal, metabolic and Endocrine:

Clonidine produces reduction in renovascular resistance and leads to diuresis. It causes a reduction in plasma catecholamine cincentrations and plasma renin activity. Alpha adrenergic stimulation of clonidine produces increases in blood sugar concentrations(27).

Dose for various routes of administration

Oral : 2-5 mcg/kg

Intramuscular: 2 mcg/Kg

Inravenous: 1-3 mcg/Kg

Intrathecal: 75-150 mcg

Epidural: 1-2 mcg/kg

Administration

Clonidine can be given through many routes including oral, intravenous, intramuscular, transdermal, epidural, intrathecal and rectal. It can be given as a continuous infusion also where the dose maybe extremely variable. The usual dose for continuous infusion is 100 mcg/hour. It can also be given by nebulization(22). Owing to its low molecular weight and high lipid solubility, it can be easily absorbed through the skin.

Clonidine gets distributed most to the kidney, gut and liver and also to the brain where its concentration is low but higher than in the plasma.

Side Effects:

Dryness of the mouth has been reported in 50% of patients. Clonidine is laso responsible for dose related sedation, depression, fluid retention and constipation [24]. Life threatening rebound hypertension and tachycardia has been reported after rapid withdrawal of the drug [27]. An unusual complication, colonic pseudo obstruction(Ogilive's syndrome), secondary to high dose clonidine infusion for the treatment of delirium tremens has been reported[26].

Uses of clonidine in anaesthesia

1) **As a premedication**

   The clonidine premedication dose ranges from 2-5 mcg/kg according to different studies[2728].

Chandrasekariaih et al in 2001 were able to show that clonidine premedication was able to counteract haemodynamic changes of pneumoperitoneum in laporoscopic cholecystectomies[29].

Kaladzija et al demonstrated significantly less stress response in patients undergoing surgery following clonidine premedication[30].

Poutlu et al observed attenuation of haemodynamic response following intubation in breast surgery patients who received clonidine as a premedication[31].

Marchal et al noted a reduction in fentanyl and isofluoran requirements in patients undergoing ENT surgery[32].

Friedberg et al demonstrated lower requirements of propofol for office based surgeries in patients who had received clonidine as a premedication[33].

In their review article on clonidine in paediatricanaesthesiaBergendahl et al concluded that clonidine is a good alternative as a premedication to midazolam in infants and children [34].

Shivinder Singh et al in their prospective randomized single blinded comparative study in adult patients undergoing laproscopic surgery reported that administration of oral clonidine 150 microgram is a simple and cost effective form of premedication in this group of patients and results in improved perioperative haemodynamic stability, reduction in requirements of anaesthetic agents and postoperative analgesia [35].

Kahoru et al in their study of 72 children regarding oral clonidine premedication concluded that there is a reduction in the MAC for tracheal intubation of sevoflurane.[36]

Ghazipour A et al [37], Indrakumari et al [38] reported reduce reduced bleeding and better visualization of surgical fiel during ENT surgery after oral premedication with clonidine.

2) To induce controlled hypotension during surgery to reduce bleeding

Woodcock TE at al demonstrated reduced isoflurane requirements to induce hypotension in patients undergoing ENT surgeries[39].

Anvari et al conducted a randomized control trial that was double blinded where remifentanyl was used for pain relief and they were able to show reduced blood loss and remifentanyl requirements in patients undergoing lumbar spine surgery in patients who received clonidine as compared to the control group, even though there was no increase in satisfaction of operating surgeons on the surgical field.[40].

Ebnesshahidi et al showed lesser bleeding following clonidine premedication in patients who had a caesarean section under general anaesthesia[41].

3) **To reduce the incidence of perioperative myocardial ischaemia**

Talke et al reported the beneficial use of clonidine in attenuating hypertensive reflexes during endotracheal intubation and thus reduces perioperativeischaemia[42].

4) **As an adjunct in regional anaesthesia**

Tamsen et al were able to demonstrate the usefulness of clonidine as an adjunct in epidural anaesthesia[43]

Clonidine has been shown to increase the duration of sensory blockade and reduce the the amount and concentration of local anaesthetic needed for regional anaesthesia[44].

5) **Sedative agent in ICU**

Recently clonidine has been used as an analgosedative in the critical care unit in both ventilated and spontaneously breathing patients[24]. The earliest reported use of clonidine in the ICU was for the treatment of sympathetic overactivity seen in the autonomic dysfunction that was present in a case of tetanus in 1989 [45]. Turner et al also demonstrated the successful use of clonidine along with other agents in the control of autonomic crisis in a patient with severe tetanus [46]. It can also be used in varied scenarios in the ICU like management of hypertension, delirious syndromes, and withdrawal syndromes following the addictive use of alcohol, opioid and nicotine[4748].

It can serve as a beneficial agent to facilitate weaning in patients who have been ventilated for long periods of time and in prevention of resistance to opioids and benzodiazepines[49].

6) **Use in deaddiction:**

Studies have shown the usefulness of clonidine in controlling autonomic and psychological symptoms of alcohol and opioid withdrawal[44,45] .

Dexmedetomidine

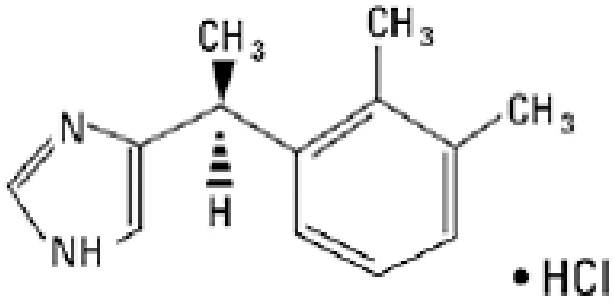
Dexmedetomidine is an imidazole compound and an active D-isomer of meditomidine which is the methylated derivative of etomidine. Like other alpha 2 agonists it also has an imidazoline chain. AS it belongs to the class of alpha 2 receptor agonists, it is chemically related to clonidine, but it eight times more specific for alpha 2 adrenoreceptors with alpha 2: alpha 1 selectivity ratio of 1620:1, compared with 200:1 for clonidine especially for 2A subtype, which makes it more effective than clonidine for sedation and analgesia. The Food and Drug Administration(FDA)initially gave dexmedetomidine its approval in the USA in 1999 for use in humans. When initially introduced it was indicated for sedation and analgesia of patients being ventilated in an ICU setting on a short term basis. Later it was accepted in other European countries as well.

As far as itsanaesthetic use is concerned, it was only in 2008, that it was introduced for sedation and analgesia of patients undergoing surgery. Its use as an adjunct for general and regional anaesthesia and as a post operative sedative and analgesic are comparable to the those of the Benzodiazepine group of drugs, but a closer analysis reveals that dexmedetomidine has more beneficial properties. Its effect are reversed by a selective alpha 2 antagonist atepimazole[50].

Chemical formula

(+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole mono hydrochloride

Chemical structure



The molecular weight of dexmedetomidine is 236.7. The pH of dexmedetomidine ranges from 4.5-7. It is a water soluble drug. The pKa of dexmedetomidine is 7.1. The partition coeeficient in octanol:water at a pH of 7.4 is 2.89[51].

Dose:

1 mcg/kg as a bolus over 10-30 minutes followed by an infusion at 0.2-0.7 mcg/kg/hr

Mechanism of action

The mechanism of action of dexmedetomidine is uniquely different from other sedatives in clinical practice. Its action at presynaptic alpha 2 receptors found in the locus ceruleus leads to diminished norepinephrine release. This is the cause for its hypnotic and sedative effects. It also reduces transmission of nociceptive impulses bringing about analgesia.

Post synaptic activation of alpha 2 receptors by dexmedetomidine leads to a fall in sympathetic activity with a resultant fall in blood pressure and heart rate. Stimulation of

CNS alpha 2 receptors also enhances vagal activity on the heart. Alpha 2 receptor activation in substantia gelatinosa inhibits nociceptive neuron firing and hence reduces substance P release. This is how dexmedetomidine produces sedation, analgesia and anxiolysis.

Pharmacokinetics of dexmedetomidine

The metabolism of dexmedetomidine follows zero order kinetics, ie every hour a constant amount of the drug is eliminated from the body and not a constant fraction of the drug within the body, which is what happens to drugs that follow first order kinetics[52]. After intravenous administration in adults dexmedetomidine has an onset of action after approximately fifteen minutes. Peak concentrations are usually achieved within one hour of an intravenous dose. Distribution half life of dexmedetomidine is 6 minutes. Its volume of distribution is 118 litres[53]. Following an intravenous injection it has an elimination half life of 1.5 to 3 hours and clearance is 39 litres/hour. Total plasma clearance is age dependant, so similar rates of infusion can be used in children and adults to attain a steady state plasma concentration. But, in patients over the age of 65 years, a higher incidence of hypotension and bradycardia has been noted. So, it may be prudent to use a less dose in this age group. In children less than two years, the volume distribution at steady state is higher, warranting use of increased doses to attain steady state. But elimination half life is prolonged which can lead to drug accumulation with time.

Following an infusion of dexmedetomidine its elimination half life can extend from 2-24 hours depending on the duration of the infusion.(25) Its bioavailabilty is more when given transdermally ie 88% , whereas it is only 73% when given in the intramuscular route[54].

The drug is bound to serum albumin and alpha 1 glycoprotein to the extent of 94% and remains constant inspite of varied concentrations of the drug. This bound fraction is reduced in patients with liver disease warranting a reduced dose in hepatic dysfunction.

Metabolism is in the liver where it gets hydroxylated through glucuronidation and undergoes biotransformation by cytochrome P450 enzyme and undergoes renal excretion in the form of glucuronide and methyl conjugates.(27). There is no known or active toxic metabolite. But in severe liver disease hepatic clearance may be reduced by as much as 50% of normal. No differences have been reported between healthy patients and patients with renal dysfunction. 95% of dexmedetomidine is excreted in the kidneys whereas only 4% is eliminated in the faeces. There is a theoretical concern that accumulation may occur with prolonged administration, since majority of the metabolites are eliminated in the urine.

Pharmacodynamics

Haemodynamic effects

After the initial bolus dose , it takes about 25 minutes for peak sedative levels to occur. Interestingly, a transient biphasic, dose dependant haemodynamic response can be observed with dexmedetomidine use. The initial 1 mcg/kg bolus dose of dexmedetomidine causes a very transient increase in blood pressure, with reflex bradycardia. This phenomenon is seen more often in younger and healthy subjects. This is due to stimulation of alpha 2b receptors in smooth muscles of the blood vessels is postulated to be the reason for the rise in blood pressure.

This increase in blood pressure can be attenuated by a slower administration and by avoiding the bolus administration of dexmedetomidine. This response lasts for five to ten minutes and is

succeeded by a minimal drop in blood pressure due to the inhibition of central sympathetic outflow. The presynaptic alpha 2 receptors are also stimulated, whereby norepinephrine release is reduced leading to a drop in blood pressure and heart rate. The dose dependant bradycardic effect of the drug is essentially mediated by the reduction in sympathetic tone and to some extent by baroreceptor reflex and enhanced vagal action.

So the haemodynamic effects of dexmedetomidine can be predicted and derived from the alpha 2 adrenoreceptor characteristics. Slow bolus administration or avoiding bolus loading to circumvent initial hypertension and reflex bradycardia, as well as modification of drug dose, rate of drug administration, adequate volume replacement and appropriate patient selection and monitoring ensures that dexmedetomidine is a drug with predictable side effects and a wide safety margin.

Haemodynamic stability achieved with dexmedetomidine compared with clonidine is related to the fact that it is more selective to alpha 2 adrenoreceptors and both baroreceptor reflex and heart rate response to a vasopressor are well preserved with dexmedetomidine.

Central Nervous System Effects:

Similar to the other alpha 2 agonists, dexmedetomidine also ensures sedation, hypnosis, anxiolysis, amnesia and analgesia. The dose dependant sedative or hypnotic effect of the drug has been extensively investigated in many experimental and clinical studies. With higher doses of dexmedetomidine, profound anaesthetic effects have been noted, even leading to the notion that it can be used as a total intravenous anaesthetic.

It is interesting to note that, dexmedetomidine induced sedation is akin to natural sleep pattern. This corresponds to other findings from studies on rats, which suggested that dexmedetomidine converges on a natural sleep pathway that causes endogenous non rapid eye movement sleep

leading to its sedative effect. This is because of release of norepinephrine when the locus ceruleus is hyperpolarized by dexmedetomidine. This is in contrast to the sleep pattern normally associated with use of other sedatives like opioids and benzodiazepines[55]. Cerebral blood flow pattern similar to natural sleep is maintained.

The amnestic effect of the drug is much less than that of the Benzodiazepine group of drugs which leads to enhanced anterograde amnesia that might lead to confusion on emergence. Unlike benzodiazepines, amnesia with dexmedetomidine is attained only at high plasma levels ≥ 1.9 ng/ml, without any retrograde amnesic effect.

The analgesic properties of dexmedetomidine in humans are more complex. It has been postulated that the spinal cord is probably the major site of analgesic action of dexmedetomidine. The analgesic effect of dexmedetomidine can be at the spinal cord level and at supra spinal sites. It may also exert anti nociception via non spinal mechanisms. Eg intra articular administration of the drug during knee surgery enhances post operative analgesia as compared to the intravenous administration of the same drug. The mechanisms postulated are activation of alpha 2a receptors, inhibition of the transmission of nerve signals through C and Aδ fibres and the local release of encephalin.

Studies done on rats have shown that the anti-nociceptive effect of dexmedetomidine can be blocked by the use of alpha 2 agonists. It has been shown that dexmedetomidine also acts on alpha 2 receptors in the spinal cord as well[56].

Respiratory Effects:

Inspite of intense sedative properties dexmedetomidine is associated with minimal respiratory effects even when administered to attain plasma levels up to fifteen times the normal levels attained

following a therapeutic dose, hence it has a wide safety margin. Respiratory response to hypercapnia is preserved and the apnoea threshold is actually lowered.

Unlike other sedative infusions of drugs like opioids, benzodiazepines or propofol, a dexmedetomidine infusion can be continued safely during a tracheal extubation and beyond. Even though dexmedetomidine does not cause respiratory depression, it was initially approved by the FDA only for use in already intubated and ventilated patients. But by 2008, the FDA had given approval for use of dexmedetomidine for sedation in procedures on non intubated patients.

Metabolic Effects:

Aho et al were able to prove that dexmedetomidine does attenuate the stress response of intubation as these patients had much lower intraoperative cortisol levels compared to patients who didn't receive dexmedetomidine as well as reducing isoflurane requirements in surgery[57].

Uyar et al noted that plasma levels of cortisol and glucose were elevated significantly in the control group compared to the dexmedetomidine group during craniotomies[58].

Mukhtar et al demonstrated that dexmedetomidine inhibited the hyperglycaemic response during surgery as compared to the placebo group in their study, hence showing an ability for the drug to attenuate the surgical stress response[59] .

A.G Yacout et al, in their study on levels of pro inflammatory cytokines like Interleukin 6 follwing major abdominal surgery were able to demonstrate significantly lower levels of IL 6 post operatively in the dexmedetomidine group as compared to the placebo group[60].

Intracellular cAMP concentrations stimulate the release of IL 6 during stressful periods. It is believed that dexmedetomidine induced stimulation of alpha 2 receptors leads to inhibitory feedback and reduced activity of adenylyl cyclase enzyme[6162].

Dexmedetomidine, through its activity on alpha 2b receptors found in the thermoregulatory centre of the hypothalamus, is known to suppress shivering. When combined with pethidine, dexmedetomidine given in low doses is known to lower the shivering threshold.(28)

Easley et al performed an open label prospective study on children and found that 0.5 mcg/kg single IV bolus over 3-5 minutes was effective in the management of post anaesthesia shivering[63].

Gastrointestinal effects:

In contrast to opioids, it does not reduce gut motility and it has a significant effect in reducing post operative nausea and vomiting

Toxicology and Side Effects

Currently the teratogenic effects of dexmedetomidine has not been adequately investigated, but the drug is known to cross the placenta and its use in pregnancy is warranted only if the benefits outweigh the risk to the fetus. No studies concerning side effects have been conducted in children[64].

Considering its actions on alpha 2 receptors, the most common side effect of dexmedetomidine is bradycardia and hypotension. If the drug is used in higher concentrations, there is a potential for pulmonary and systemic hypertension and direct or reflex bradycardia.[65,66]Bradycardia has been reported in up to 40 percent of healthy patients post operatively. But this temporary bradycardia and hypotension can be easily treated with the use of atropine, ephedrine and fluid replacement. Hence care must be taken while using this drug in patients who are hypovolaemic, have left ventricular dysfunction or have severe heart block. However severe bradycardia leading to cardio-pulmonary arrest has been documented with the use of dexmedetomidine.[67,68] A detailed analysis of these reports may have been responsible, finally leading to asystole. Nevertheless these case reports cannot be ignored even if dexmedetomidine cannot be held accountable for the fatal effect. Hence one must be cautious and choose patients appropriately when choosing to use dexmedetomidine in the critically ill for sedation because this subset of patients will have complicating factors like negative chronotropism.

Other known side effects are nausea, bradycardia, atrioventricular blocks or atrial fibrillation and hypoxia. Overdose can cause first degree or second degree atrioventricular block. Many of these will be noted either during or briefly after the initial bolus dose, and may be avoided by increasing the time duration over which the bolus is given

Uses of dexmedetomidine

a) As a premedication
b) As a general anaesthesia adjunct to reduce emergence delirium and post operative pain, to attenuate the stress response associated with surgery and anaesthesia (intubation,

extubation, emergence). When used as an adjunct to general anaesthesia, dexmedetomidine can decrease the minimum alveolar concentration (MAC) requirement of inhalational anaesthetic agents and provide opioid sparing properties up to 90%.[69] This unique property is advantageous in situations where high anaesthetic concentration is undesirable. Eg certain neurosurgical procedures, minimally invasive endoscopic procedures and ambulatory anaesthesia.

c) Adjuvants to prolong sensory and motor blockade following regional anaesthesia.

d) Sedation in monitored anaesthesia care

e) To induce controlled hypotension in surgeries to reduce blood loss.

f) Sedation in the mechanically ventilated patients in ICU.

g) Paediatric procedural sedation

h) Awake fibre optic intubation: Dexmedetomidine is an ideal drug in this situation, without causing respiratory depression in addition to providing a dry field due to its anti-sialogogue property.

i) Cardiac anaesthesia:

In patients with pulmonary hypertension undergoing mitral valve replacement it will reduce both SVR and PVR[70]. The beneficial properties of dexmedetomidine render it useful in the current era of early extubation and fast tracking of cardiac surgery patients.

j) Bariatric surgery: Hoffer et al reported the successful use of dexmedetomidine infusion with significant reduction of opioid requirements postoperatively in a morbidly obese patient weighing 433 kilograms with obstructive sleep apnoea and severe pulmonary hypertension with no respiratory depression[71].

k) Perioperative and off label use:

1)Total intravenous anaesthesia: This is an innovative application of the beneficial effects of dexmedetomidine as a total intravenous anaesthetic agent in patients with difficult airways.(Partly supplemented with local anaesthetics)[72]

2)Sedation during awake craniotomies [73]. Regional anaesthesia with dexmedetomidine used for sedation and analgesic effect at the same time providing haemodynamic and respiratory stability allows arousal and interaction with the patient to facilitate neurological evaluation in awake craniotomy and awake carotid end arterectomy[7475].

3)Control of supraventricular and junctional tachyarrythmias with dexmedetomidine has been reported by Chrysostomou et al in a retrospective paediatric case series study [76].

4) Cheol Lee et al demonstrated theantihyperalgesic effect of dexmedetomidine on high dose remifentanyl induced hyperalgesia . They postulated that this happens because dexmedetomidine decreases spinal tyrosine phosphorylation of the NR2B subunit of the NMDA receptor[77].

Organ protective effects:

Myocardial ischemia and cardioprotection:

The perioperative stress response is characterized by sympathetically mediated tachycardia and hypertension which can be ameliorated by alpha 2 adrenoreceptor agonists. This haemodynamic stabilization by alpha 2 agonists can lead to a reduction in the episodes of perioperative myocardial ischemia[78]. But there are theoretical concerns against the use of these drugs due to their vasoconstricitve and hypotensive properties which can potentially lead to ischaemia.

At present protection against myocardial ischemia and improved outcomes in patients who are at risk of cardiac events has only been demonstrated for clonidine. Currently there is only evidence of the beneficial effect of dexmeditodine in the perioperative haemodynamic management of patients undergoing vascular surgery[79]. Hence more studies are needed to establish whether dexmeditmdine can confer a myocardial protective effect and reduce post operative mortality in the same way as clonidine does .

Neuroprotection:

Neuroprotective properties of dexmedetomidine have been demonstrated in various experimental models of cerebral ischaemia where they have shown an attenuation of hypoxic ischameic brain injury in developing brains that are vulnerable to neuronal damage. Significant functional and neurological improvement after brain injury was also noted. The exact mechanism of how dexmedetomidine confers neuroprotection is unknown, but it is possible that it is due to its effect on modulating the release of neurotransmitters in the central and peripheral nervous system[80].

Renal protection:

By inhibiting the action of vasopressin(AVP) at the collecting ducts through alpha 2A receptors, alpha 2 agonists exert a diuretic effect with decreased salt and water reabsorption[81]. Also, by acting on alpha 2B receptors , there is increased osmolal clearance through non AVP dependantpathways. Studies have shown that dexmedetomidine preserve cortical blood flow and hence attenuates murine radiocontrast nephropathy[82]. There is also evidence that it reduces murine

ischaemia reperfusion injury. However, more prospective studies on humans are needed to establish a renal protective effect beyond doubt.

Ghodki et al were also able to demonstrate a 30% reduction in the requirement of isoflurane to maintain anaesthesia in surgeries where a dexmedetomidine infusion was used[83].

Keniya et al conducted a study that showed that dexmedetomidine infusions intraoperatively definitely reduced isoflurane requirements to maintain anaesthesia, reduced stress response to intubation and reduced the need for further analgesics[84].

Fragen RJ et al conducted a prospective randomized placebo controlled study and demonstrated a 17% reduction in requirement of sevoflurane with dexmedetomidine in patients undergoing surgery[85].

Bloor BC et al demonstrated that after a two minute infusion of dexmedetomidine , there was an initial increase in MAP followed by a longer lasting decrease in MAP[86].

Ayoglu et al in their study determined the effectiveness of dexmedetomidine in reducing bleeding and intraoperative opioid requirement during septoplasty surgery under general anaesthesia[87].

Suvadeep Sen et al were able to show that propfol requirements were rduced by 48% for induction and 61% for maintenance in patients undergoing spine surgery when dexmedetomidine was used[88].

Gonul T Keles et al conducted a double blinded randomized control trial and showed that a dexmedetomidine- desflurane anaesthetic combination was superior to a dexmedetomidine-sevoflurane combination in spine surgeries with respect to extubation time and recovery in the PACU[89].

Overall dexmedetomidine possesses unique properties that make it an attractive agent for both anaesthesiologist and intensivists.

Sevoflurane

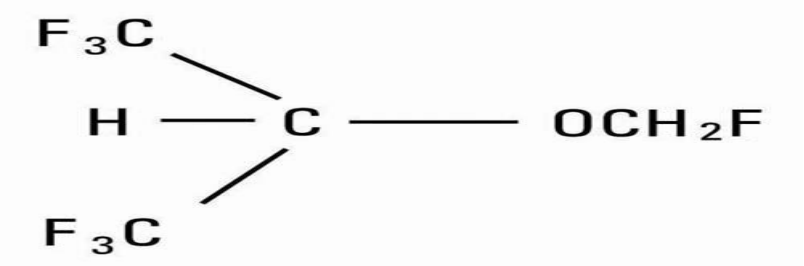
Sevoflurane is a halogenated methy propyl ether, this is being used as a general anaesthetic drug for both induction and maintenance of anaesthesia. Sevoflurane was discovered by Ross Terrell. It was synthesized in 1968 and reported in 1971. . It has been named so because it seven fluorine atoms in its substituent's. Initial development and introduction into anaesthetic use was slow due to some apparent toxic effects found during the experimental stage, which were late attributed to a flawed experimental design. It was first introduced into clinical practice in Japan in 1990.

It is one of the most commonly used inhalational anaesthetics, finding widespread use especially in day care procedures and in paediatric anaesthesia and along with desflurane is fast replacing the use of isoflurane and halothane in clinical practice today. Its non pungency and fast build up in alveolar concentration make it an ideal agent for inhalational induction. Because of its low blood solubility, there is a rapid fall in its alveolar concentration following discontinuation of the agent and patients wake up faster too.

Chemical name

fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether

Chemical structure:



Physical properties:

Sevoflurane is a clear, colourless liquid, which is sweet smelling, non pungent and nonflammable and nonexplosive. The Minimum Alveolar Concentration value of sevoflurane in adults is 2% in oxygen .The MAC, in common with other volatile agents, is higher in children (2.6%) and neonates (3.3%) and it is reduced in the elderly (1.48%).Sevoflurane is not corrosive to aluminium, steel, brass or copper. It is a stable compound and stored in amber coloured bottles.

Its physical constants are:

1)Molecular weight: 200.05

2)Boiling point at 760 mm Hg: 58.6$_{o}$ Celsius

3)Specific gravity at 20 degrees Celsius: 1.520-1.525

4)Vapour pressure in mm of Hg: 157 mm of Hg at 20 degrees Celsius

Distribution Partition Coefficients at 37°C:

Blood/Gas	0.63 - 0.69
Water/Gas	0.36
Olive Oil/Gas	47 – 54
Brain/Gas	1.15

Uptake and Distribution:

The blood gas partition coefficient of sevoflurane is 0.69, which is approximately half that of isoflurane and close to that of desflurane which is 0.42. Hence the rate of equilibration between alveolar and inspired concentrations of sevoflurane is faster than isoflurane, but not as fast as desflurane. It is non irritant to the upper airways of the respiratory tract and this also contributes to its faster rate of induction of anaesthesia.

Effects on organs systems:

Cardiovascular system:

Sevoflurane mildly depresses the contractility of the heart. It does not reduce systemic vascular resistance or arterial pressure as much as isoflurane or desflurane does. Because it does not cause an increase in the heart rate, cardiac output is not as well maintained with sevoflurane as with desflurane and isoflurane. But this results in lower myocardial oxygen demand. It is a less potent coronary arterial dilator and therefore does not appear to cause the phenomenon of coronary steal.

Respiratory system:

Sevoflurane is non irritant to the upper airways of the respiratory tract. Sevoflurane causes depression of respiration characterized by reduced tidal volumes just like isoflurane does, reduces respiratory drive inresponse to hypoxia and leads to increased partial pressures of carbon dioxide. This ventilator depressant action could be because of central depression of medullary respiratory neurons and depression of diaphragmatic contractility and function. It relaxes bronchial smooth muscle and hence reverses bronchospasm.

Cerebral Effects:

Sevoflurane use leads to slightly increased cerebral blood flow and increased intracranial pressure. But this effect is very minimal at MAC ranges of 0.5 to1. It reduces the metabolic oxygen requirements of the brain.

Neuromuscular:

Sevoflurane provides adequate relaxation for intubation of the trachea following inhalational induction in children. Just like the action of isoflurane, sevoflurane also potentiates the action of non depolarizing neuromuscular blockers to a similar extent.

Renal and Hepatic Effects:

Sevoflurane is known to reduce renal blood flow mildly but overall it is well preserved. The peak concentration of serum fluoride following sevofluraneanaesthesia is similar to that following enfluoraneanaesthesia. The concentration of serum fluoride is directly proportional to the duration of exposure to sevoflurane. Fluoride concentrations can go up to micromoles/litre. However renal toxicity does not seem to be related to inorganic fluoride concentrations in the blood. This maybe due to such rapid elimination of sevoflurane that not much is available for metabolism in vivo.

It also reduces blood flow in the portal vein but also increase blood flow in the hepatic artery, thus maintaining the final blood flow to the liver.

Emergence Delirium:

Emergence delirium also called emergence agitation is an often noted phenomenon especially in children immediate post operatively. It has been noted with varied drugs like benzodiazepines, barbiturates and inhalational anaesthetics especially with sevoflurane. Emergence delirium is defined as a dissociated state of consciousness in which the child is inconsolable, irritable,

uncompromising or uncooperative, typically thrashing, crying, moaning, or incoherent [909192]. There might be additional paranoid behavior. Sometimes the children will not be able to identify familiar people or objects.

Parents witnessing this behavior will claim that the behavior is unusual for the child. Although generally self limiting (5-15 min) ED can be severe and may result in physical harm to the child and particularly the site of surgery.

There have been many studies dealing with emergence delirium in patients receivingsevoflurane. Emergence delirium occurs in approximately 19.3% of children receiving sevofluraneanaesthesia. The mean duration of these delirious episode was 6.9 +/- 7.8 minutes. Younger patients with greater levels of preoperative anxiety seemed to be more susceptible to emergence delirium [93].

Biotransformation and toxicity:

Approximately 5% of the absorbed dose of sevoflurane is metabolized by the 2E1 isoform of liver microsomal enzyme P-450 which can be induced by phenobarbital, isoniazid and ethanol and inhibited by disulfiram.The major breakdown product is hexafluoroisopropanol, which is an organic fluoride molecule that is excreted in theurine as a glucuronide conjugate. Although this molecule is potentiallyhepatotoxic, conjugation of hexafluoroisopropanol occurs sorapidly that clinically significant liver damage seems theoreticallyimpossible. The second breakdown product is inorganic fluoride ion .Fluoride levels exceed 50 micro moles/ litre in about 7% of patients but usage of sevofluraneanaesthesia is not associated with significant renal impairment.

Alkali present in CO2 absorbents like soda lime and barium hydroxide lime can interact with sevoflurane and break it down into 5 compounds that are named A,B,C,D and E. However in clinical situations it is largely Compound A and to a lesser extent Compound B that are produced. These breakdown products are believed to be toxic in rats, leading to damage to the kidneys, liver and brain. into a toxic compound called compound A(fluoromethyl-2,2-difluoro-1-[trifluoromethyl]vinyl ether) which has been shown to be nephrotoxic in rats. Increased Compound A levels are associated with increased respiratory gas temperatures, low flow anaesthesia, dry barium hydroxide, increased levels of sevoflurane concentration and longe durations of anaesthetics.

On interaction with metal and environmental impurities that can be found in the industrial packaging process, sevoflurane can get degraded into hydrogen fluoride. If this comes into contact with the mucosa of the respiratory tract, it can lead to acid burns. This risk has been substantially reduced by adding water to sevoflurane during the manufacturing process and packaging it in special plastic containers.

Lin EP et al were able to show combination of sevoflurane administration and mild hypothermia conferred long term protection in cerebral hypoxic ischaemia in a modified neonatal mouse model[94]

Kharasch et al were able to show that moderate duration anaesthesia with sevoflurane during which compound A formation occurs is as safe as low flow isofluraneanaesthesia when conventional measures of hepatic and renal function and more sensitive markers of renal tubular cell necrosis were used to assess hepatic and renal function[95]

Monitoring the Depth of anaesthesia

Horace Wells was not successful in his attempt to demonstrate the usefulness of Nitrous Oxide as an anaesthetic in 1845 because during his demonstration where he administered Nitrous Oxide to a patient for a dental extraction, the patient screamed out in pain. But after the operation, on questioning the patient, he was not able to remember the sensation of pain, ie he had memory loss with the anaesthetic but not loss of pain sensation. One year later W.T.G Morton was able to successfully anaesthetize a patient with ether. The patient however, later recounted that even though he had no pain , he was aware of the surgery in progress . Awareness under anaesthesia is a concept that has come to recognition only recently and it is quite a scary proposition for any patient undergoing surgery. Since the days of Horace Wells and WTG Morton, however, modalities of assessing depth of anaesthesia have come a long way.

Methods of monitoring depth of anaesthesia

Depth of anaesthesia can be measured by either of these methods:

a)Clinical methods

b)Brain electrical activity monitoring

Clinical methods

Clinical signs:This includes evaluation of clinical signs like checking for movements, whether the patient is responding to commands, perspiration, tearing etc.

Isolated fore-arm technique: This method was practiced earlier. A tourniquet was applied to the upper arm before administration of the muscle relaxant. Movement of the hand to commands, or spontaneously or in response to skin incision was considered as a sign of awareness.

Lower esophageal contractility: Even after the administration of muscle relaxants , the lower esophagus retains its potential contractility. This contractility is related to the amount of CNS depression and hence is used to assess anaesthetic depth.

Heart rate variability: It is postulated that anaesthetics act first on the brain stem and then only on the cortex of the brain. Therefore measuring an important autonomic activity like heart rate that is mediated by the brain stem and not affected by any other factor other than the anaesthetic agent is a good method for assessing anaesthetic depth.

Brain electrical activity monitoring:

Electrical activity in the brains of animals was first noted in England by Richard Caton in 1875. In 1920 the development of amplifiers allowed the recording of this low voltage electrical activity in the brain. Since then it has been know that anaesthetic drugs affect EEG. The recording of spontaneous electrical activity of the brain is known as Electroencephalogam. All the anaesthetic agents can cause changes in electrical cortical activity which will be reflected as change in EEG. But unprocessed raw EEG is not a useful tool for assessing depth of anaesthesia.

Hence Different techniques and various modalities have been developed to process and analyse this raw EEG. One such monitor is the Bi spectral index(BIS) monitor which has found widespread application in anaesthesia for neurosurgery.

The bispectral index is a statistically based, empirically derived complex parameter. It is a weighted sum of electroencephalographic subparameters, including a time domain, frequency domain and high order spectral subparameters.It is a reproducible, objective, observer independent, quantitative measure of hypnotic state. The BIS monitor provides a single dimensionless number, which ranges from 0 (equivalent to EEG silence) to 100 (equivalent to fully awake and alert). A BIS value between 40 and 60 indicates an appropriate level for general anaesthesia.

BIS Monitor

Some characteristics of BIS monitoring of EEG include:

a)It is a more advanced EEG processing approach than the traditional fast fourier technology.

b)It correlates greatly with clinical data like patient movements, haemodaynamics and concentration of anasthetic drug.

c)BIS is more sensitive to the hypnotic component of the activity of the anaesthetic agent and less sensitive to the analgesic effect of the anaesthetic drug being used.

d) Using BIS can definitely improve anaesthetic management.

BIS has been shown to correlate well with many commonly used anaesthetic drugs. It is preferred to sensory or motor responses as it is a standard and FDA approved monitor for monitoring anaesthetic depth, and it is also more convenient for anaesthetists to use. It shows a good correlation with end tidal sevoflurane concentration as well as measured blood propofol concentrations. It has also been shown to reduce the consumption of anaesthetic agents and hence results in faster awakening and faster discharge.

The BIS monitor has a non invasive sensor that is stuck in a particular fashion across the forehead. It has an adhesive strip on the back, like a typical EEG pad. This sensor will pick up EEG signals and send that information through the cable to the BIS engine. This engine will then process this data according to a specified algorithm and provide the user with a BIS index.

BIS Sensors

There have been clinical studies where the anaesthetic sparing effect of dexmedetomidine was studied and demonstrated using almost only haemodynamic criteria to assess adequacy of depth

of anaesthesia. However, as alpha 2 agonists are drugs that causes sympatholytic effects, looking at autonomic responses like heart rate and blood pressure to assess depth of anaesthesia may not be reliable [96].

Glass et al have shown that using a BIS monitor for anaesthesia can excellently predict depth of anaesthesia when using propofol, midazolam, alfentanyl and isoflurane to conduct anaesthesia[97].

Kearse et al demonstrated usefulness of BIS in predicting haemodynamic response during laryngoscopy and intubation[98].

Punjasawadwon Y et al conducted a randomized control trial and were able to show that BIS guided anaesthesia was able to reduce the incidence of awareness in pateintsintraoperatively in pateints who are at high risk for intraoperative awareness[99]

BIS monitoring has been reported to facilitate immediate recovery and reduced consumption of anaesthetics[100].

Materials and Methods

Materials and Methods

Study Setting:

Our study was conducted in both, neurosurgical and orthopaedic operating room of our institution.

Study Design

An open labeled randomized control trial was conducted to compare the efficacy of oral clonidine premedication with intraoperative infusion intravenous dexmedetomidine on sevoflurane requirement, haemodynamics and recovery time in patients undergoing two to four level of instrumented spinal fusion.

Study population:

a) Inclusion criteria:

Adult ASA I and II patients between the ages of 18 and 60

b) Exclusion criteria:

1) Patients below the age of 18 and above the age of 60 years

2) ASA III and IV patients

3) Patients with liver dysfunction

4) Patients with creatinine of more than 1.5 mgs%

4) Patients with the history of allergy to the study medication.

5) Pregnant patients

6) Patients undergoing scoliosis surgery or more than 5 level of fusion

Method of randomization:

Computer generated randomization table was made to randomize the patients.

Primary outcome:

Efficacyof oral clonidine premedication versus intraoperative infusion of dexmedetomidine on sevoflurane requirement in patients undergoing major spine surgery.

Secondary outcomes:

Effect of these interventions on haemodynamic stability, time to recovery from anaesthesia and blood loss during surgery.

Study Period:

The study was conducted over a period of 4 months from May to August of 2014.

Target sample size and rationale:

The sample size was calculated based on the study "comparing the effects of oral clonidine premedication with intraoperative dexmedetomidine infusion on anaesthetic requirement and recovery from anaesthesia in patients undergoing major spine surgery".[101]The mean and standard deviation of end tidal sevoflurane concentration was used to calculate the sample size. The formula used is

$N= 2(z1-\alpha/2 +z1-ß/2)\sigma2 / \delta2$

σ 2 = pooled standard deviation of the groups which were compared.

SD(g1) =0.17, SD(g2) =0.12

S2 =Effect size = (x1-x2)2

X1= mean of g1=0.86, x2= mean of g2= 0.72.

Z1-α/2=1.96 where α= error is taken as 5%

Z1-ß/2=0.84, where1-ß = power = 80%

A sample of 20 in each arm is needed to detect the difference of 0.14 mean end tidal sevoflurane concentration between the two groups with an error of 5%and power of 80%

Selection of study patients:

After getting the clearance from the Institutional Review Board and the Ethics committee, the study was commenced. Patients scheduled for two to four levels of instrumented spinal fusion (both, thoracic and lumbar) were included in the study. All the patients were seen in the pre-anaesthesia clinic and assessed by a qualified anaesthesiologist and given clearance for the planned surgery. Those patients who met the eligibility criteria of the study were approached on the day before the surgery by the primary investigator, and they were explained about the study intervention in detail in their own language and consent was obtained. Premedication orders were written on the chart by the principal investigator according to the randomization number. 31 patients were approached, out of 31, 26 patients were enrolled in the study. Patients were randomized in to two groups, Group 1 and Group 2. Patients in Group 1 received tablet clonidine 200 µg as a premedication 30 to 45 min prior to the surgery (Clonidine group). Patients in Group

2 received 1 µg/kg of dexmedetomidine as a bolus over 15 min prior to surgery followed by 0.5 µg/kg/hr of dexmedetomidine during the intraoperative period till the start of skin closure (Dexmedetomidine group).

Anaesthesia Protocol:

Premedication: Patients in Group 1 (clonidine group) received tablet clonidine 200 µg along with the Tablet Metoclopromide 10mg as a premedication 30-45 minutes prior to surgery. Those who were allocated to the Group 2(Dexmedetomidine group) received only tablet Metaclopromide 10 mg as a premedication.

The patients were identified by an attending anesthesiologist and by the nurse in the pre-operative holding area. After confirming the patient's identity, patients were then wheeled into the operating room. Under local anaesthesia, peripheral intravenous cannulation (18 or 16 Gauge) and radial artery cannulation (20 Gauge) was done. After placing the standard monitors such as non invasive/invasive blood pressure, electrocardiography, pulse-oximetry, agent analyzer and bispectral index monitor (BIS), patients in Group 2 received dexmedetomidine bolus through a separate 22 G peripheral line in a dose of 1 µg/kg over ten minutes. Five hundred ml of crystalloid (0.9%Nacl or ringer's lactate) was given during the bolus administration of dexmedetomidine.

Syringe pumps used for the infusion:

Induction and maintenance:

Patients were induced with 2 µg/kg of fentanyland 1.5 mg/kg of propofol. If further propofol is required, it was given in 10 mg increments till the loss of verbal response. Then the patients were paralysed using vecuronium in a dose of 0.1mg/kg. Following three minutes of mask ventilation the patient's trachea was intubated. Haemodynamic changes were noted during intubation and immediately following intubation. The patients were then proned. Soon after the proning, the

patients in the Group 2 (dexmedetomidine group) was started on an infusion of dexmedetomidineat the rate of 0.5 µg/kg/hour and continued till the beginning of skin closure. Haemodynamic changes associated with proning were then noted. Anaesthesia was maintained with 50 % oxygen, 50% air with the total fresh gas flow of one litre, and sevoflurane. End tidal Sevoflurane concentration was titrated to maintain the BIS value of 40-50. Total dose of morphine upto 0.1 mg/kg was given incrementally over the first half an hour. One gram of intravenous paracetamol was given for additional analgesia.

Patient's haemodynamics including systolic,diastolic and mean arterial pressure and heart rate were recorded every 15 minutes after proning till the end of surgery. End tidal concentration of sevoflurane (Et Sevo), Minimum Alveolar concentration (MAC) of sevoflurane and BIS reading were also recorded at 5, 15,30 minutes,1,2,3 hrs. Blood pressure was targeted to be within 20% of baseline value. Hypotension was defined as 10% drop from the low target value and hypertension as 20% rise from the upper target value. Hypotension was treated with 5 mg of ephedrine if the heart rate was less than 60 or 50-100 mcg of phenylephrine if the heart rate was more than 60. Episodes of hypertension was treated first with 0.5 mg/kg of propofol.If there was a persistent hypertension for more than 1 minute after the propofol bolus, 0.5 µg/kg of fentanyl was given. Episodes of bradycardia (<60/min) was noted, also the number of episodes of bradycardia associated with hypotension which needed treatment with either with atropine or glycopyrrolate were noted. Muscle paralysis was maintained with intermittent doses of vecuronium while monitoring the Train of Four (TOF) with the use of nerve stimulator. All patients received 4 mg of ondansetron at the start of skin closure. End tidal Sevoflurane concentration was reduced to half while starting of skin closure and cut off during the halfway of skin closure. The time of stopping the sevoflurane was noted. Fresh gas flow was not altered till the patient was turned supine. After

turning the patient to supine,the fresh gas flow was then increased to 6 litres and neuromuscular block was reversed with 0.05 mg/kg of neostigmine and 10µg/kg of glycopyrrolate. Once the patients were awake and satisfying the extubation criteria, the trachea was extubated and time of extubation was noted. The time of stopping the Sevoflurane to the time of extubation was noted as recovery time. It was measured using a timer in the anesthesia machine and noted down in minutes.

Total dose of fentanyl and propofol used intraoperatively, blood loss during surgery, duration of surgery, and time taken for recovery, all were noted.

Monitor (Philips MP50- Intellivue) used during the study period:

Statistical analysis

All demographic, haemodynamic parameters such as heart rate, blood pressure, and anaesthetic requirements, episodes of hypertension, hypotension and bradycardia, duration of surgery, time for awakening, and blood loss between two groups were compared. The mean, standard deviation and frequency with percentages were calculated.

The statistical analysis was performed using independent sample t-test. P value < 0.05 was considered statistically significant. The descriptive statisticswas done using mean along with standard deviation. The outcome comparison between the two groups over time was analysed using repeated measure of ANOVA. The line plots was given based on mean and standard deviation values.

RESULTS

RESULTS

Demographics:

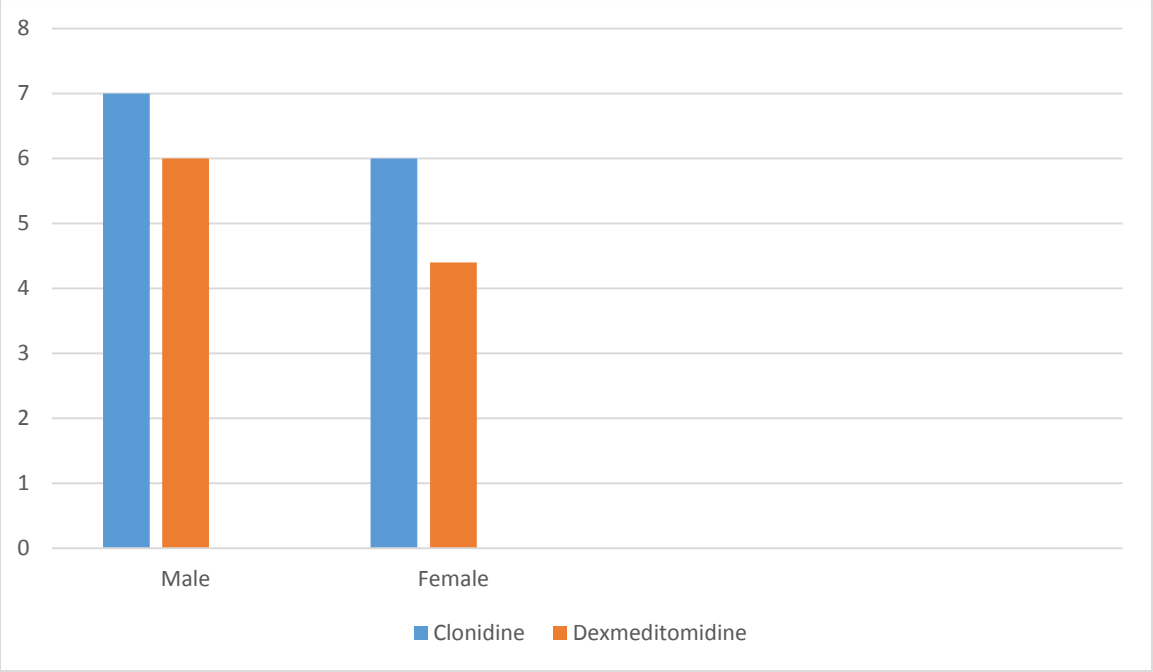
The demographic data such as age, sex, weight of patients in both the groups were shown in Table 1.

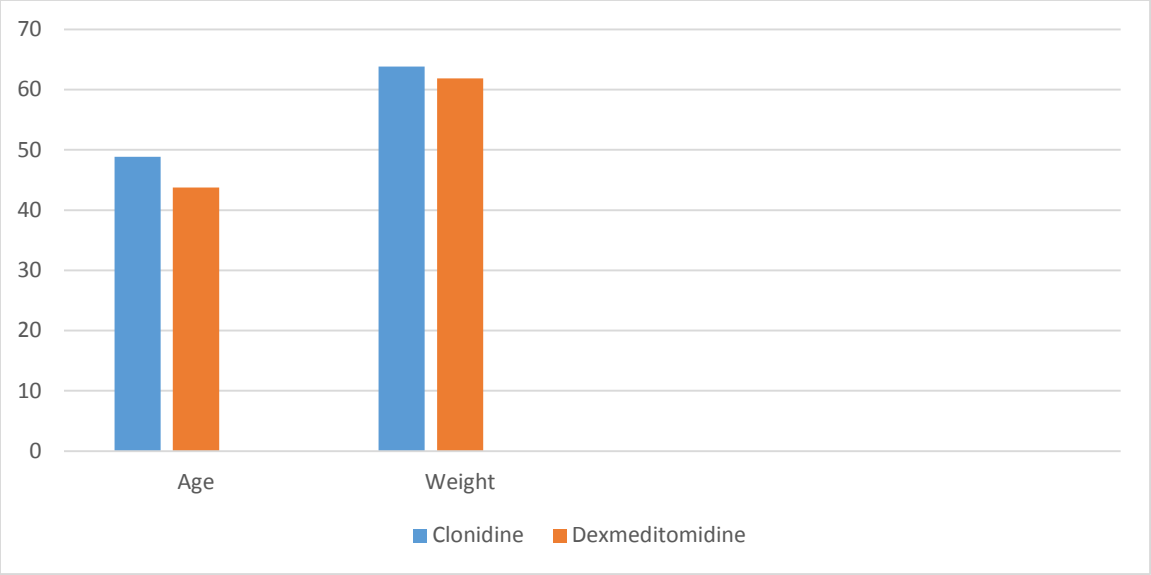
Table 1: Demographic Data

Character	**Group1 (Clonidine)**	**Group 2 (Dexmedetomidine)**
Total no. of patients	13	13
Age in Years (mean±SD)	48.84 ± 6.92	43.76 ±13.35
Sex(M/F)	7/6	6/7
Weight in Kg (mean±SD)	63.84 ± 10.11	61.84 ± 11.86
ASA Grading(I/II)	7/5	11/2

No statistically significant difference was found with respect to age, sex, weight or ASA Grading between the two groups.

Figure 1: Demographics





End Tidal Sevoflurane concentrations at various time intervals during the study period:

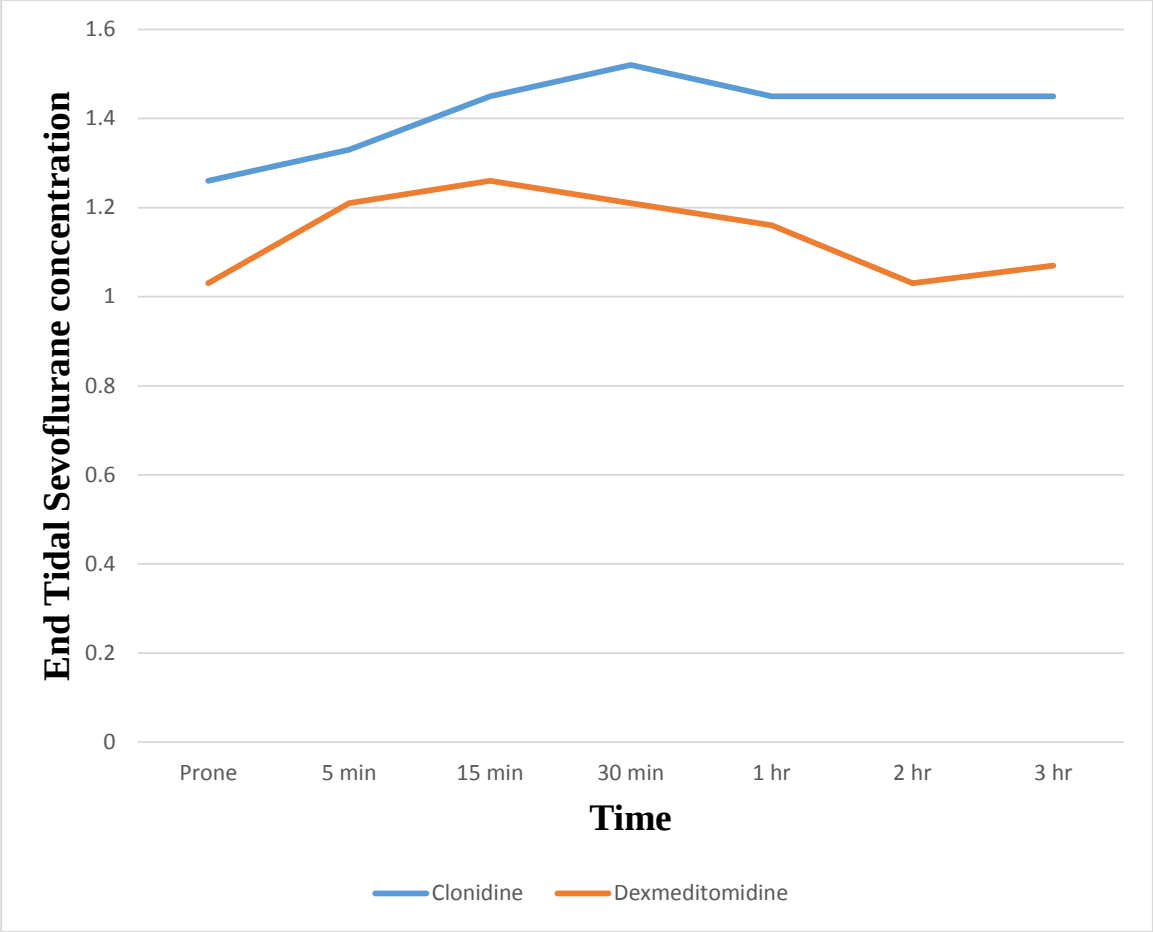
Table 2: End Tidal concentration of Sevoflurane at various time periods:

Time	Group 1 Clonidine (mean(SD) of Et sevo)	Group 2 Dexmedetomidine (mean(SD) of Et Sevo)	P value
At prone position	1.26(0.38)	1.03(0.37)	0.13
5 minutes	1.33(0.36)	1.21(0.26)	0.38

15 minutes	1.45(0.29)	1.26(0.20)	0.02
30 minutes	1.52(0.25)	1.21(0.18)	0.0016
1 hour	1.45(0.14)	1.16(0.16)	0.0001
2 hours	1.45(0.15)	1.03(0.09)	<0.001
3hours	1.45(0.18)	1.07(0.07)	<0.001

The end tidal sevoflurane concentration required to maintain a BIS value between40-50 was measured at various time intervals throughout the procedure. It was found that there was no difference in requirement of sevoflurane concentration during the first 10 minutes after proning. However, there was a significant difference in the End tidal sevoflurane concentration between the two groups at 15 minutes(P value=0.02), 30 minutes(P value= 0.0016), 1 hour(P value= 0.0001), 2 hours(P value<0.001) and 3 hours(P value<0.001) after prone positioning. Therefore it was found that the requirement of sevoflurane was considerably lower in the dexmedetomidine group when compared to clonidine group during the intraoperative period.

Fig. 2: End Tidal Sevoflurane concentrations



Recovery Time:

Recovery time was defined as, the time interval from stopping of the sevoflurane to the time of extubation.

Table 3: Recovery time between the two groups:

	Group 1 (Clonidine)	Group 2 (Dexmedetomidine)	P value
Recovery time (Mean (SD) in minutes)	10.81(3.33)	8.97(2.86)	0.21

The time taken for recovery was 10.81 minutes in the clonidine group (Group1), whereas it was 8.97 minutes in the dexmedetomidine group (Group 2). However, this was not statistically significant. (P value= 0.21). The recovery time was not delayed with both clonidine and dexmedetomidine.

Heart rate:

The heart rate was monitored throughout the duration of the surgery and noted down at various intervals.

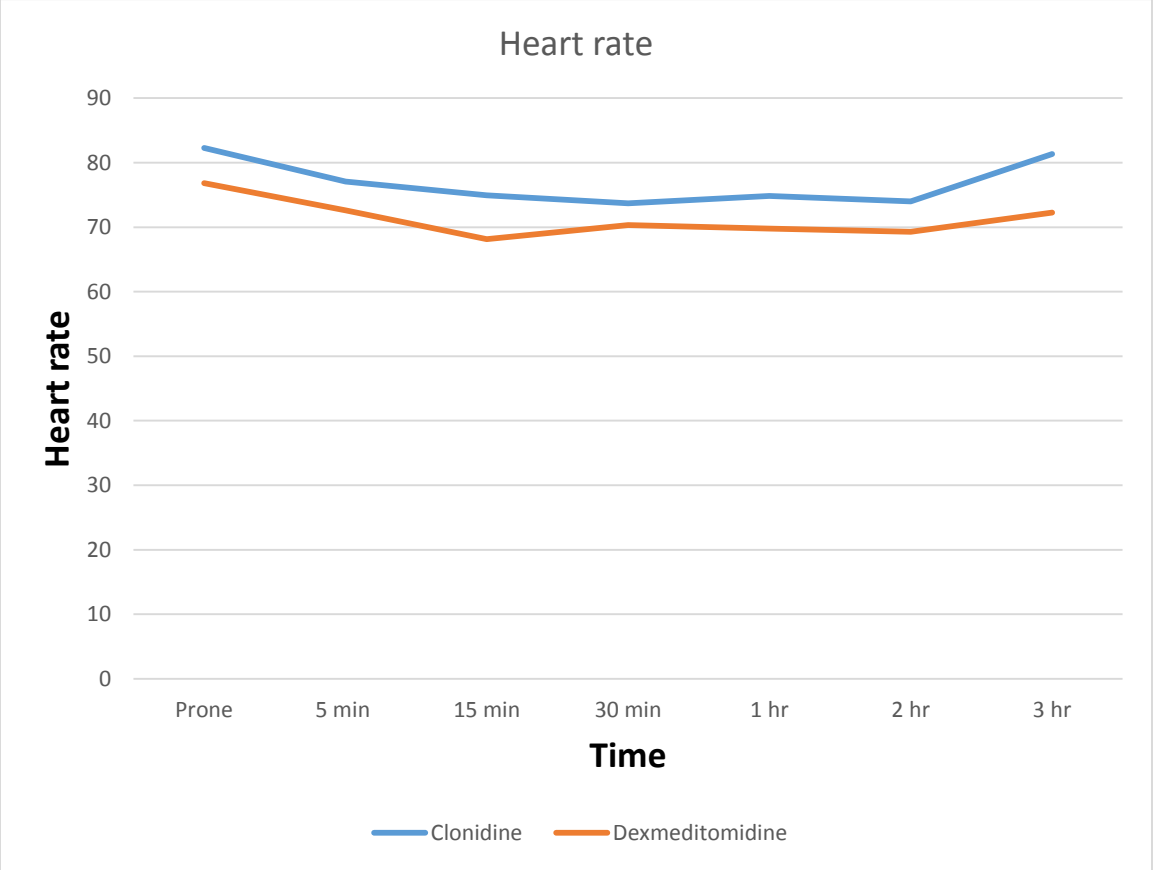
Table 4: Heart rate at various time intervals during the study period:

Time interval	Group 1 (Clonidine) Mean(SD) of HR/min	Group 2 (Dexmedetomidine) Mean(SD) HR/min	P value

Prone	82.30(13.00)	76.84(13.45)	0.30
5 minutes	77.07(13.43)	72.61(10.97)	0.36
15 minutes	74.92(12.33)	68.15(8.74)	0.11
30 minutes	73.69(11.48)	70.31(8.77)	0.32
1 hr	74.84(8.84)	69.76(7.21)	0.12
2 hr	74(6.80)	69.38(8.61)	0.14
3 hr	81.33(11.64)	72.25(2.62)	0.04

It was noticed that the heart rate in the dexmedetomidine group was consistently lower at all time intervals as compared to the clonidine group. However, the difference was not statistically significant at all times except at 3 hrs.

Fig. 3: Heart rate response at various time intervals between the two groups:



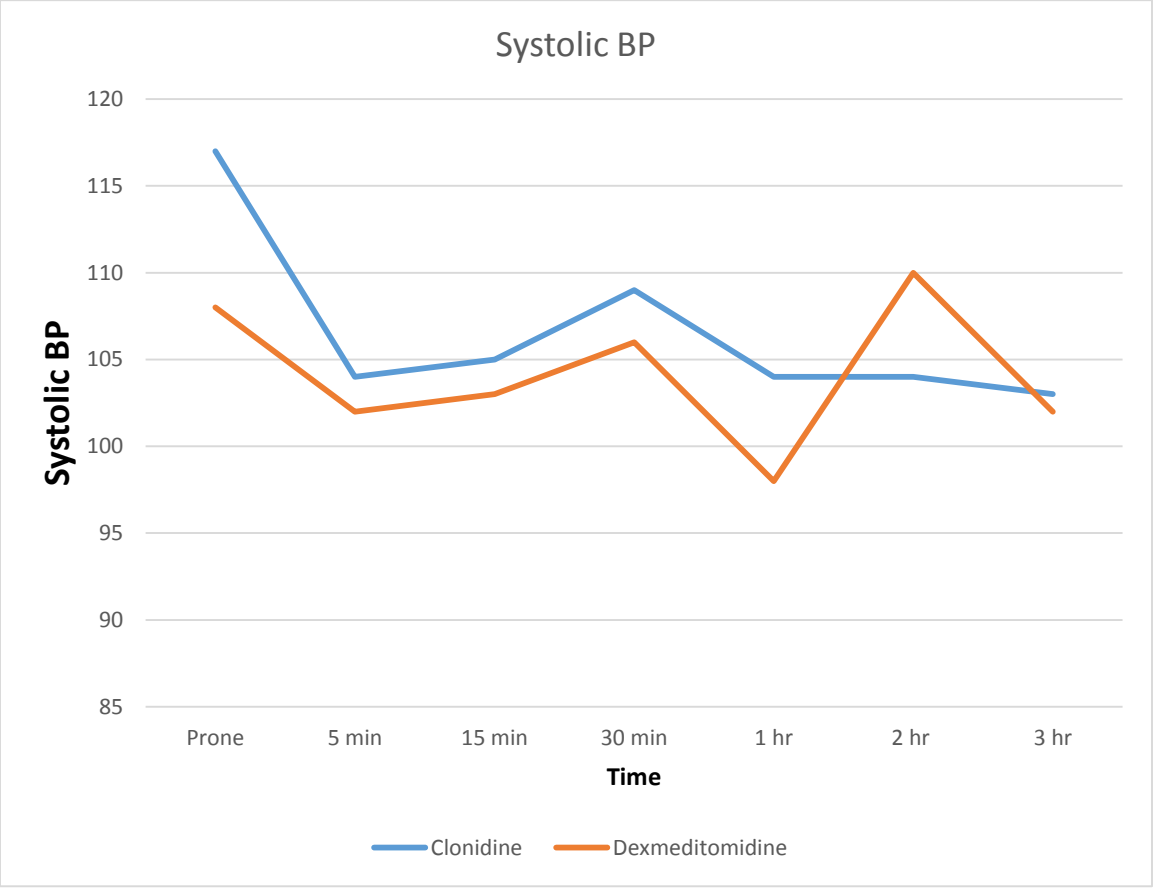
Systolic Blood Pressure:

Table 5: Systolic Blood pressure at various time intervals during the study period between the two groups:

Time Intervals	Group1 Clonidine Mean(SD) in mmHg	Group2 Dexmedetomidine Mean(SD)in mmHg	P value
Prone	117.76(20.71)	108.53(17.03)	0.22
5 min	104.92(19.20)	102.31(13.23)	0.70
15 min	105.54(21.20)	103.31(10.56)	0.83
30 min	109.62(13.36)	106.15(12.55)	0.57
1 hr	104.30(11.98)	98.46(7.90)	0.15
2 hr	104.76(10.57)	110.07(7.87)	0.15
3 hr	103.16(7.57)	102.08(11.30)	0.78

There was a drop in the systolic BP from the baseline by 8.59% in the clonidine group, when compared to 10% drop in the dexmedetomidine group during the prone position. However this difference was not statistically significant. . There was no difference in systolic BP between the two groups throughout the surgery.

. Fig 4: Sytolic Blood Pressure at various time interval during the study period between the two groups:



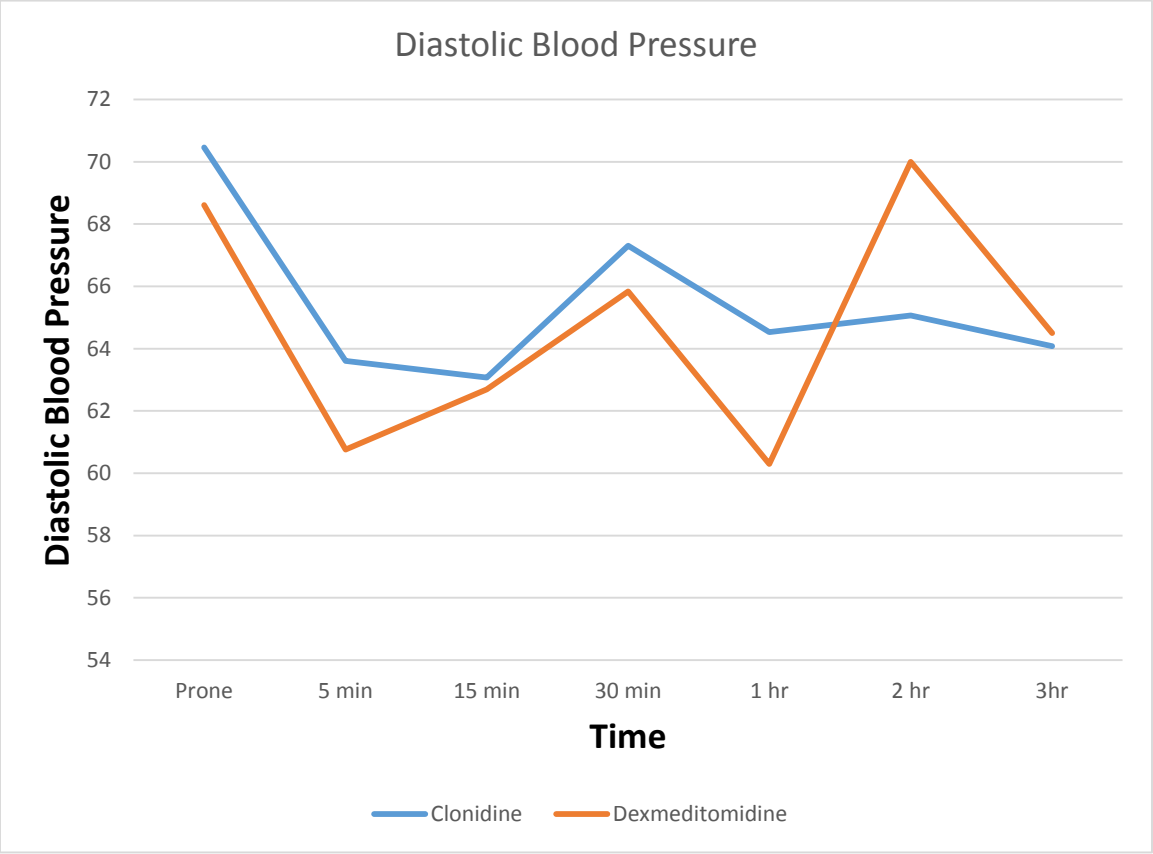
Diastolic Blood Pressure:

Table 6: Diastolic Blood Pressure at various time interval during the study period:

Time Interval	Group1 Clonidine Mean(SD)in mmHg	Group2 Dexmedetomidine Mean(SD)in mmHg	P Value
Prone	70.46(14.44)	68.61(13.02)	0.73
5 min	63.61(10.50)	60.76(13.12)	0.54
15 min	63.07(7.31)	62.69(8.34)	0.90
30 min	67.30(7.59)	65.84(9.03)	0.65
1 hr	64.53(7.24)	60.30(6.56)	0.13
2 hrs	65.07(8.84)	70(9.01)	0.10
3 hrs	64.08(10.55)	64.5(12.32)	0.92

In the clonidine group, there was a fall in diastolic BP of 14% from baseline values while proning. Whereas, in the dexmedetomidine group, this fall in BP was 12.82% from the baseline. There was no significant difference in diastolic BP between the two groups at various time intervals.

Fig 5: Diastolic blood pressure at various time intervals during the study period:



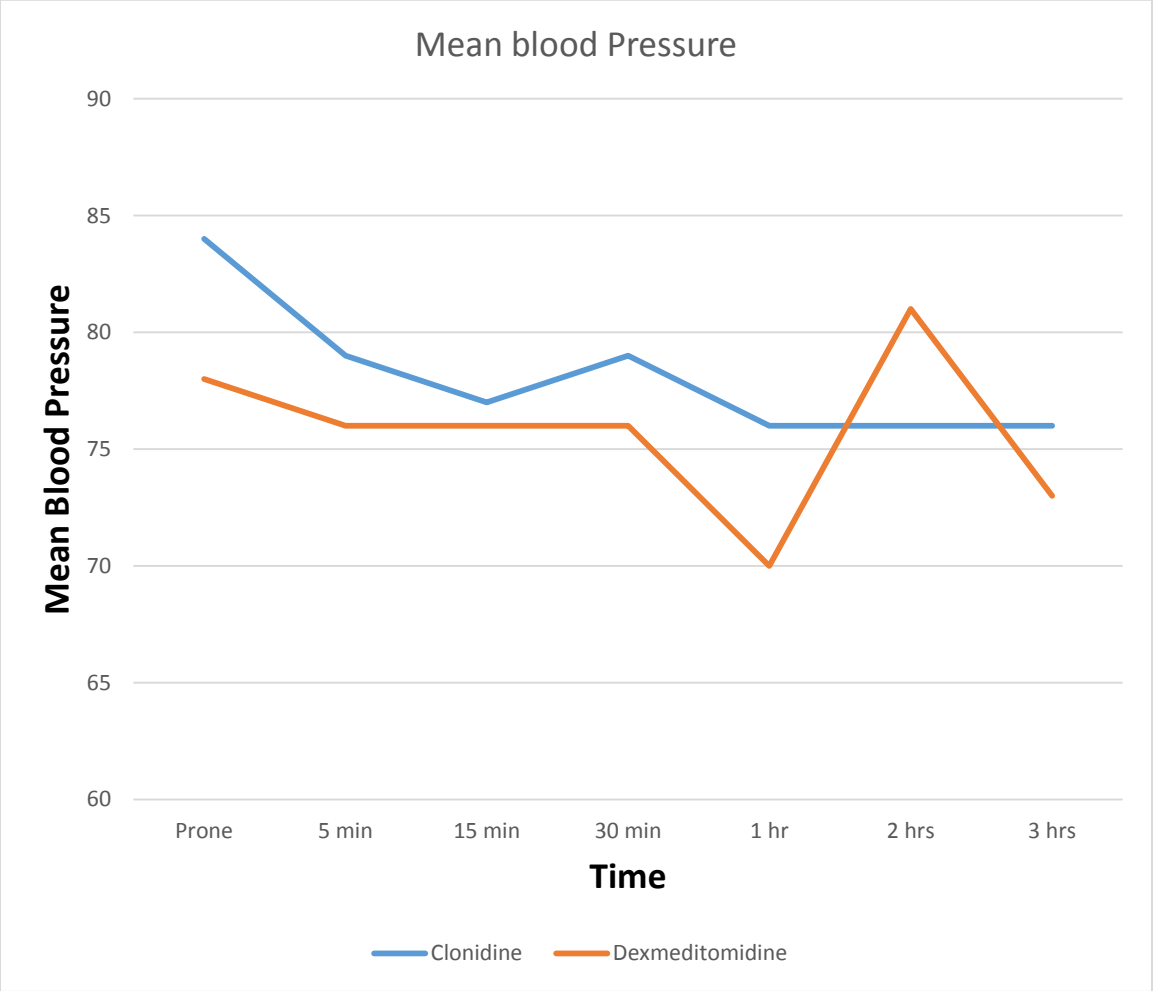
Mean Blood Pressure:

There was no statistical difference in the Mean BP between the two groups at various time intervals.

Table 7: Mean Blood Pressure at various time intervals during the study period:

Time intervals	Group1 Clonidine Mean(SD) in mmHg	Group 2 Dexmedetomidine mean (SD) in mmHg	P value
Prone	84.61(15.71)	78.84(12.34)	0.30
5 min	79.61(7.69)	76.15(8.56)	0.28
15 min	77.69(12.83)	76.69(15.03)	0.34
30 min	79.61(7.69)	76.15(8.56)	0.28
1 hr	76.84(8.54)	70.23(5.81)	0.30
2 hrs	76.76(8.31)	81.23(6.77)	0.14
3 hrs	76.16(8.08)	73.33(11.66)	0.49

Fig 6: Mean Blood Pressure at various time intervals:



Haemodynamic changes during Intubation:

We have noted the heart and blood pressure changes at the time of intubation in both the groups to compare the efficacy of these drugs on attenuating the stress response to intubation.

Table 8: Haemodynamic response during intubation:

	Group 1 Clonidine Mean(SD)	**Group 2 Dexmedetomidine Mean(SD)**	**P value**
Heart rate at intubation (beats/min)	86.31(15.53)	70.15(13.35)	0.01
MAP at intubation (mmHg)	91.54(16.13)	79.31(15.72)	0.057

It was found that there was a significant difference in the heart rate at intubation with mean heart rate in the dexmedetomidine group being 70.15, whereas the mean heart rate in the clonidine group was 86.31. The mean MAP in the clonidine group was 91.54 and it was 79.31 in the dexmedetomidine group, with a P value of 0.057. Dexmedetomidine was better for attenuating the intubation response when compared to clonidine.

Total Propofol requirement during the maintenance phase:

The amount of additional propofol administered to the patients in the two groups in the maintenance phase of anaesthesia during periods of increased BP was also noted. No statistically significant difference in propofol requirement was found between the two groups. The mean propofol dose given during maintenance phase in the clonidine group was 38.07(30.85), while the mean propofol dose of the dexmedetomidine group was 30.38(35.44) and the P value was 0.56.

Table 9: Total Propofol requirement during the maintenance phase:

	Group 1 Clonidine Mean(SD)	**Group2 Dexmedetomidine Mean(SD)**	P value
Total Propofol dose (mg)	38.07(30.85)	30.38(35.44)	0.56

Total Fentanyl requirement during the maintenance phase:

Fentanyl was administered during the hypertensive response if it was not controlled with propofol. The amount of fentanyl required during the maintenance phase was noted to compare the analgesic sparing effect of two drugs.

Table 10: Total Fentanyl requirement during the maintenance phase

	Group 1 Clonidine Mean(SD)	**Group2 Dexmedetomidine Mean(SD)**	**P value**
Fentanyl dose(µg)	35.77(30.20)	25(28.28)	0.32

There was no difference in requirement of fentanyl between the two groups during the maintenance phase ($p = 0.32$)

Intraoperative Blood loss:

At the end of the surgery, an estimate was made of how much blood was lost during the course of the procedure to see if either of these drugs can decisively reduce blood loss as compared to each other.

Table 11: intraoperative blood loss:

	Group 1 Clonidine Mean (SD)	**Group2 Dexmedetomidine Mean (SD)**	**P value**
Blood loss (ml)	411.53(89.33)	367(114.28)	0.28

Although the mean blood loss in the dexmedetomidine arm was less compared to the clonidine arm this was not significant both statistically (P value = 0.28) and clinically.

Incidence of Bradycardia:

Number of episodes of bradycardia (HR< 60/min) was noted in both the groups. Also the episodes of severe bradycardia associated with hypotension which needed treatment with atropine also noted. Out of the 13 patients in the clonidine arm, two patients developed bradycardia ie 15.38% of the patients. In the Dexmedetomidine group, out of thirteen patients, 7 patients (53.84%) had episodes of bradycardia. None of the patients had severe bradycardia (HR< 40/min) associated with hypotension which needed treatment with atropine in either groups.

Table 12: Incidence of bradycardia between the two groups:

Number of episodes of bradycardia	**Clonidine group** **No. of patients (%)**	**Dexmeditomidine group** **No. of patients (%)**
0	11(84.61%)	6 (46.15%)
1-5	2(15.38%)	7(53.84%)

Episodes of Hypotension:

The number of episodes of hypotension in each patient was noted in both arms of the study. Hypotension was defined as a fall in MAP of 30% from the baseline MAP. There were five or

more episodes of hypotension in three out of the thirteen patients in the clonidine group ie 23%. In the dexmedetomidine group however, this number was seven out of the thirteen patients ie 55%. Episodes of hypotension were treated with boluses of ephedrine or phenylephrine along with fluid bolus. Patents in dexmedetomidine group had more episodes of hypotension which needed treatment with vasopressors compared to clonidine.

Table 9: Number of episodes of hypotension between the two groups:

No. of episodes of hypotension	**Group 1** **Clonidine** **Number (%)**	**Group 2** **Dexmedetomidine** **Number (%)**
0	5(38%)	4(30%)
1-4	5(38%)	2(15%)
≥5	3(23%)	7(55%)

DISCUSSION

DISCUSSION

Anaesthetizing a patient for spine surgery imposes a lot of challenges for the anaesthesiologist. Most patients who come for spine surgery will have chronic pain on multiple medications; providing an adequate pain relief without any adverse effects is a challenge. Most of them are elderly with multiple co-morbidities and with autonomic instability. Maintaining the haemodynamic stability with adequate amount of anesthetics without causing awareness is a major challenge. Also these surgeries are associated with wide fluctuation in blood pressure and can cause significant blood loss, providing a bloodless field without compromising the blood supply to vital organs is a next challenge. Providing anaesthesia for early high quality recovery to detect neurological deficit without wide fluctuations in heamodynamics, and discomfort due to pain and shivering and post operative nausea and vomiting is a major task for the anesthesiologist.

Alpha 2 adrenergic agonists are currently being extensively investigated in anaesthetic practice because of their sympatholytic, haemodynamic stabilizing, analgesic and anaesthetic sparing properties and good recovery properties.

This study was conducted to compare the effect of oral clonidine premedication with intraoperative dexmedetomidine infusion on sevoflurane requirement. . Secondary outcome of our study was to compare the recovery time, intraoperative haemodynamics, analgesic sparing effect and to compare the blood loss between the two drugs.

We compared the two drugs given though different routes because:

1) Oral clonidine has an bioavailability of 75-100%. Its onset of action is within 30-60 minutes and peak action is at ninety minutes. Hence it is as effective as the intravenous form of clonidine.

2) The oral form of clonidine is very easy to administer, while the intravenous form has to be given as a slow IV infusion while monitoring the vitals.

3) In our institution oral Clonidine is often used as a premedication drug in spine surgery and endoscopic sinus surgery and surgeries where controlled hypotension is needed, provided, there is no contraindication for using this drug. So we wanted to compare it with the newer alpha 2 agonist dexmedetomidine.

4) Since dexmedetomidine is shorter acting (1-2 hrs) as compared to clonidine (8-12hrs), and it is available only as intravenous preparation, we decided to administer dexmedetomidine as a bolus 15 minutes before surgery followed by an infusion throughout the intraoperative period.

Effect of the two drugs on anaesthetic requirement

In our study, we used a BIS monitor on all the patients and titrated the anesthetic concentration of sevoflurane being administered by keeping the BIS score between 40-50. We found that there was a significant difference in sevoflurane requirement between the two groups during the intraoperative period. The dexmedetomidine group required significantly less sevoflurane as compared to the clonidine group to maintain the same depth of anaesthesia from 15 minutes to 3 hrs after proning the patient . There was no change in sevoflurane requirement during the first ten minutes; this can be explained by the fact that, it is practically difficult for the anesthesiologist to adjust the sevoflurane concentration while stabilizing the patient in prone position during this

period.Another theory is that, the peak effect of intravenous dexmedetomidine starts half an hour after the bolus administration. After 15 mins of proning the peak effect of dexmedetomidine could have reduced the anaesthetic concentration.

In our study, we did not have a placebo arm to compare and say, the percentage reduction of sevoflurane (anesthetic sparing effect) by dexmedetomidine and clonidine. The mean age of our patients were 48 and 43 in group 1,2 respectively. If we take the end tidal concentration of sevoflurane to maintain 1 MAC is considered to be 1.7% for adult with 40-50 yrs of age, then our study showed that the clonidine had produced 15% reduction in sevoflurane requirement at 1, 2 and 3 hours after proning, whereas the dexmedetomidine group had produced a 32%, 40% and 38% reduction in sevoflurane requirements at 1,2 and 3 hours respectively.

Studies have shown that perioperative administration of dexmedetomidine reduces the sevoflurane requirements in children undergoing various surgeries[102,103,105]. The sedative, hypnotic and analgesic properties of dexmedetomidine can reduce the dose of hypnotics, analgesics and anaesthetics required to be administered intraoperatively[104]. A prospective double blind randomized controlled trial by Na Young Kim et al have shown that intraoperative dexmedetomidine infusion reduced sevoflurane requirement while maintaining a BIS score of 45-50 and also reduced emergence agitation without delaying recovery in children undergoing ambulatory surgery[115]. In their study they used a loading dose of 1 mcg/kg, followed by a maintenance dose of 0.1µg/kg/hr. They were able to show a 23-67% reduction in the requirement of dexmedetomidine as compared to the control group who received saline instead of dexmedetomidine.

Several studies done on adults undergoing abdominal surgery under general anaesthesia supplemented with dexmedetomidine at the rate of 1 mcg/kg bolus followed by an infusion at the rate of 0.4-0.6 mcg/kg/hr decreased the end tidal sevoflurane (ET Sevo) by 27.3 to 33% [105,106,107.] Patel et al showed that ET Sevo can be reduced up to 41.6% with dexmedetomidine at the rate of 2 mcg/kg bolus followed by 0.7mcg/kg/hr infusion in pediatric tonsillectomy patients with obstructive sleep apnoea syndrome when compared with intra operative fentanyl bolus [97]. The anaesthetic sparing effects of dexmedetomidine may vary according to thedexmedetomidine dose, type of surgery, age group of patients and type of anaesthetics or analgesics used cocurrently[100,104] Supplemental drugs like dexamethasone and acetaminophen can influence the additive analgesic effect of dexmedetomidine and sevoflurane[97]. Similar to other studies, this study also demonstrated that dexmedetomidine reduces the sevoflurane requirement by 30-40%.

Shinichi Inomata et al conducted a study on the effects of clonidine premedication on sevoflurane requirement and anaesthetic induction time in 104 ASA I patients and observed that premedication with oral clonidine 4.5 mcg/kg reduced the MAC-skin incision, MAC Awake and Vital Capacity rapid inhalation anaesthetic induction time (VCRII time)[108]. MAC- skin incision was found to be 65% less in the clonidine group as compared to the control. MAC Awake was 53% less in the clonidine group as compared to the control group.

In our study we have used approximately 3 µg/kg of oral clonidine and 1 µg/kg of dexmedetomidine bolus followed by 0.5 µg/kg/hr infusion. We are not sure whether both the drug doses were equivalent.

Recovery profile:

In our study, we were not able to show any significant difference in recovery time between the two groups. The mean wake up time for clonidine was 10.81(3.33) minutes and for dexmedetomidine was 8.97(2.86) minutes. Since we did not have a placebo group to say whether these drugs reduced the recovery time compared to placebo. Since,Patients in both the groups woke up within 15 minutes of cutting the inhalational agents, it has been shown that adding alpha 2 agonist as an adjuvant to general anaesthetic does not delay the recovery time. Other studies done similarly have come to the same conclusion as well.[103]

When alpha 2 agonists are used as an adjunct to general anaesthetics, in addition to reducing the Minimum Alveolar Concentration requirement of inhalational anaesthetic agents and providing opiate sparing properties it enables better recovery profile in terms of earlier awakening.[109]Gupta et al in their study of children undergoing spinal surgery reported that the subjects in the dexmedetomidine group had a more favourable recovery profile, without adverse perioperative haemodynamics. They have also shown thatthe post operative nausea and vomiting also was significantly less in patients. [110]

Turan et al.[111]found that use ofdexmedetomidine improved conditionsfor extubation but did not prolong the time for recovery in patients presenting for craniotomy. Norimasa etal studied the recovery profile of dexmedetomidine as a general anaesthetic adjuvant in patients undergoing lower abdominal surgery. They concluded that postoperative cognitive function was not affected by dexmedetomidine administration.[112]Basar et al concluded that a single dose of 0.5µg/kg of dexmedetomidine given preoperatively led to significant sedation with no change in recovery scores.[122]

Gonul et al conducted a study on balanced anaesthesia in spine surgery, and came to the conclusion sevoflurane-dexmedetomidine combination showed shorter extubation times, better Aldrete criteria and Faster track criteria during recovery in the post anaesthesia care units. [88]

Time to extubation did not differ between the clonidine and placebo group in the Fehr et al [113] study although a larger dose of clonidine was used ie 4 mcg/kg. No instance of awareness during anaesthesia was noted in their study while doing the implicit and explicit memory analysis.

Mariappan et al compared the effects of oral clonidine premedication and dexmedetomidine infusion as an adjuvant with isoflurane based general anesthesia in patients undergoing spine surgery and showed that recovery profile was similar in both the groups.[103] This study also have shown that the recovery profiles are similar to Mariappan et al study.

Haemodynamic parameters during the surgery:

The haemodynamic parameters observed in our study were heart rate, systolic BP, Diastolic BP and Mean BP. Haemodynamic response during intubation and during the surgery were noted. Heart rate and mean BP were attenuated with dexmedetomidine compared to clonidine.

But during the most part of the surgery, there was no significant difference in heart rate, Systolic BP, Diastolic BP and Mean BP between the two groups. The SBP, DBP, MBP were consistently stable without wide fluctuations during the procedure in both the groups. The heart rate was always between 70-80 in both the groups during the procedure showing that use of these two drugs provided less fluctuations in haemodynamics in response to noxious stimuli.

In our study, some of the patients who received dexmedetomidine had a significant reduction in heart rate, after the bolus was given, but it was not associated with hypotension requiring atropine

or vasopressor therapy. This may be due to adequate preloading with crystalloids during the dexmedetomidine bolus administration. Also most of our study patients were ASA 1/2 physicalstatus,where patients were healthy or their medical problems were well controlled..

Studies have shown that, target controlled infusions of dexmedetomidine (0.5,0.8,1.2,2.0,3.2,5.0 and 8.0 ng/ml) reduces heart rate and blood pressure in a dose dependant fashion. All the studies done till date reported similar cardiovascular effects for these dose ranges of dexmedetomidine. Young Kim et al in their study on children where, dexmedetomidine was used in lower doses (1 mcg/kg bolus followed by 0.1mcg/kg/hr) reported significantly lower heart rate and mean arterial pressure during surgery.[114] In their study 6 out of the 20 children who showed bradycardia with or without hypotension had to be given atropine. Although haemodynamic changes vary according to dose and surgical type, haemodynamic instability may occur in minor surgery where low dose dexmedetomidine has been used in children [97,115,116,117]. However, In our study, none of the patients who received dexmedetomidine developed clinically significant bradycardia associated with hypotension that required treatment with atropine during surgery or during the immediate post operative period..

Dyck JB et al reported that intravenous administration of dexmedetomidine in a dose of 2 µg/kg over 5 minutes in volunteers led to a biphasic response with initial increase in mean arterial pressure of 22% and reduction in heart rate of 27 % during infusion followed by stabilization of mean arterial pressure at lower values than baseline and unchanged heart rate [118]. In contrast the preoperative administration of dexmedetomidine in a dose of 1 mcg/kg over a period of 10 minutes resulted in 20% reduction in heart rate and mean arterial pressure in adults [119,120].In our study, the bolus administration of dexmedetomidine in a dose of 1 mcg/kg over 10 minutes was found to be safe without any undesirable side effects like profund bradycardia or hypotension.

Yacout et al in their study of patients undergoing major abdominal surgery with intravenous dexmedetomidine infusion 1 mcg/kg bolus dose followed by 0.5 µg/kg/hr intravenous infusion reported that the heart rate and mean arterial pressure were significantly lower along with the significantly less post operativepain in the dexmedetomidine group. They also observed the recovery profile as assessed by measuring tracheal extubation time, time to eye opening, time to following verbal commands was longer in the dexmedetomidine group compared to the control group, but with no statistically different significance between the two groups [59].

Ebert et al reported that lower plasma dexmedetomidine concentrations leads to reductions in MAP, Heart Rate and Cardiac Index without changes in stroke volume, pulmonary or systemic vascular resistance [64]. Basar et al reported that a single dose of 0.5µg/kg given 10 minutes pre-induction caused a 27% reduction in Cardiac Index with significant reduction in MAP and Heart rate without changes in Stroke volume Index [121].

Chandrashekariah et al reported that oral clonidine premedication with the dose of 150 microgram which is approximately 2µg.kg body weight was able to attenuate haemodynamic turbulence due to pneumoperitoneum and reduce anaesthetic consumption of isoflurane[30]. Sung et al reported that haemodynamic stability with 150 micrograms of oral clonidine premedication during laproscopic cholecystectomy and 30% reduction in the requirement of isoflurane[122]. Mrinamoy Das et al used oral clonidine at a dose 2.7 mcg/kg and reported the same effects [123].

Analgesic sparing effect:

In our study we administered fentanyl (0.5µg/kg) during the periods of hypertension which was not controlled by propofol. However after analysis of the results it was found that there was no significant difference in fentanyl requirement between the two groups. The mean fentanyl

requirement in the clonidine group was 35.77(30.20)µg and in the dexmedetomidine group it was 25(28.28)µg. Eventhough it was lower in the dexmedetomidine group, this was not significant both clinically and statistically. Since both these drugs belong to same group and we did not have a placebo group it is very difficult to quantify the analgesic sparing effect. But it is obvious that patients needed very little fentanyl during the maintanence pahse for treating the hypertension.

Jakola et al evaluated analgesia after intravenous administration of different doses of dexmedetomidine(0.25, 0.50 and 1 mcg/kg) and fentanyl 2 mcg/kg in healthy humans and noted that dexmedetomidine had a moderate analgesic effect that was maximized at 0.5 mcg/kg [124]. In accordance with this Cortinez et al showed that 0.5 mcg/kg of IV dexmedetomidine is equivalent to 0.6 nanograms/ml of target controlled infusion which has adequate analgesic effect in healthy humans.[125] The dose of dexmedetomidine used in our study was similar to the dose mentioned in this study. Jakola et al reported that the analgesic action of dexmedetomidine was not dose dependant and had an apparent ceiling effect at 0.5 mcg/kg.[106]Although animal studies indicate that alpha 2 adrenoreceptor agonists have a dose dependant analgesic and sedation effects, studies in humans reveal that the dose response relationship is only for sedation but not for analgesia [126,127]. One plausible justification for this variation in results between the human and animal studies could be due to very high doses compared to the doses used in the human trials were used in the animal experiments. [25,100].In the current study no patients had undue sedation post operatively during extubation and in the post operative care unit when given dexmedetomidine at a rate of 0.5 mcg/kg/hr.

In the study by Fehr et al [116], clonidine did not have any additional effect in reducing intraoperative requirement of remifentanil. This is consistent with the investigation by Engelman et al [128] noting similar intra operative opioid requirements with and without clonidine. Nevertheless clonidine is known to reduce post operative narcotic requirements [129] . Because the essential site of action of clonidine is dorsal horn of spinal cord, it can be deduced that IV administered clonidine has limited analgesic effect, enabling modulation of postoperative pain, but less effective against intense intraoperative nociceptive stimulation[130].

Gupta et al in their study of children undergoing spinal surgery reported that intraoperative consumption of sevoflurane and fentanyl requirement was significantly less in the dexmedetomidine group compared to placebo group.[131]

Propofol requirements:

During the course of the surgery, we used propofol to treat the hypertension We compared the requirement of propofol during the maintenance phase in both the groups. It was found that that mean requirement of propofol in the clonidine group was 38.07(30.85) mg, whereas it was 30.38(35.44) in the dexmedetomidine group. This difference between the two groups was not significant.

Suvadeep Sen et al concluded in their study on the effect of dexmedetomidine infusion on propofol requirement for induction and maintenance of desired depth of anaesthesia on the basis of targeted BIS scores in spine surgery, that the mean requirement of propofol was found to be lessened by 48.08% and 61.8% for induction and maintenance of anaesthesia respectively. If propofol alone is used in high doses to maintain adequate depth of anaesthesia it might offset the main adavantage

of propofol ie rapid recovery. If dexmedetomidine with its multifaceted beneficial actions of sedation, analgesia and anxiolysis is added, it was found to reduce the propofol requirement[86]. Few other studies have also noted the role of dexmedetomidine in significant reduction of propofol doses required for induction and maintenance of anaesthesia. But in these studies, motor, sensory or autonomic responses were used for monitoring the depth of anaesthesia.[132133] In our study we used BIS monitor was used for the assessment of anaesthetic depth.

Fehr et al[119], in their randomized double blind randomized control study in ASA I patients undergoing superficial surgery, they reported that propofol requirements was reduced by 20% in the clonidine group where clonidine was given 4 mcg/kg intravenously during a target control infusion of propofol with monitoring of anaesthetic depth with BIS. Imai et al [134]noted reduction of propofol requirement by 40% with oral clonidine 150 mcg premedication. This was a greater reduction compared to the study by Fehr et al, although the clonidine dose was smaller, probably because propofol dosing depended on haemodynamic perturbations without monitoring of brain functions as done with BIS.

Friedburg et al observed that oral clonidine when administered in a dose of 200 mcg as a premedication produced statistically significant reduction of propofol consumption in office based cosmetic surgery [135]. Guglielminotti J. et al [136]observed that oral clonidine in a dose of 5 mcg/kg given as premedication in ASA I patients reduced intraoperative propofol requirements in comparison with 1 mg/kg of hydroxyzine without producing undesirable effects on recovery and haemodynamic stability. Morris et al, in their study in vascular surgery reported that premedication with oral clonidine 3 mcg/kg reduced the requirement for propofol which is a pharmacokinetic effect and not a pharmacodynamics central sedative effect [137].

Chaithanya Kumar et al in their study in patients have burns debridements and dressings reported that dexmeditomidne given IM in a dose 1mcg/kg given one hour before surgery, reported that it is a good anaesthetic adjuvant, reduced the requirement of propofol and attenuated sympathoadrenal response compared to the control group, maintains stable intraoperative haemodynamics, adequate duration of analgesia with an excellent recovery profile [138].

In our study, we have maintained anesthesia with air oxygen and sevoflurane and hypertensive response only was treated with propofol, both the groups needed less propofol for treating the haemodynamic response during the maintenance phase.

Blood loss:

Spine surgery is usually associated with significant hypertensive response and substantial blood loss which can intern leading to haemodynamic instability and increases the risk of autologous transfusion. Apart from avoiding the risks of homologous blood transfusion, improved visualization of the operating field, shorter operating times and maintenance of adequate perfusion of the vital organs also is very important. In the past many drugs like volatile anaesthetics, direct acting vasodilators, autonomic ganglion blockers, beta adrenergic receptor blockers and calcium channel blockers have been used successfully to reduce blood pressure intraoperatively and hence lead on to lowered levels of blood loss. But currently the focus has been shifted from controlled hypotension to provide an optimum blood pressure with the use of alpha 2 agonists to achieve a

haemodynamically stable patient with added hypnotic, analgesic and anaesthetic sparing properties in addition to their sympatholytic characteristics.

The dexmedetomidine induced stable haemodynamic profile can be attributed to the known sympatholytic effects of alpha 2 agonists. This in turn leads to reduced blood loss.

Durmus et al used dexmedetomidine ten minutes pre operatively in a dose of 1 mcg/kg followed by 0.5 mcg/kg/hr intraoperatively in tympanoplasty and septoplasty surgery, reported that dexmedetomidine reduced bleeding after assessing the bleeding score and also that it facilitated earlier recovery within the framework of haemodynamic stability.

El-Gohary et al conducted a study where they compared the efficacy of dexmedetomidine to the efficacy of sodium nitroprusside(SNP) in producing hypotensive anaesthesia in scoliosis surgery. The dexmedetomidine bolus dose used was 1 mcg/kg over ten minutes before pre-induction to be followed by 0.2-0.5 mcg/kg/hr infusion during the maintenance phase. They observed a significant reduction in blood loss and transfusion requirement in the dexmedetomidine group as compared to the SNP group. Significant lowering of HR, MAP and CI was also noted in the dexmedetomidine group as compared to the SNP group[139]. This is consistent with other studies[140141142].

Zahara Anvari et al [39], in their studied the effect of oral clonidine premedication on blood loss in spine surgery found that clonidine reduced intraoperative blood loss at the same levels of blood pressure as the placebo group. This observation is similar to the study by Okuyama et al who observed that clonidine could reduce blood loss without inducing hypotension during paranasal sinus surgery [143] and other studies performed on the same subject [144145146147]. The study conducted by ZaharaAnvari et al suggests that the reduction in blood loss is independent of its hypotensive

effects, implying that the same reduction in blood loss can be seen at higher blood pressures, hence nullifying the need for hypotensive anaesthesia.

Amrinder Singh et al studied the effectiveness of clonidine versus atenolol in providing optimal surgical field in nasal surgeries under general anaesthesia observed that by giving oral clonidine premedication of 100 mcg produced a better quality surgical field reflecting more reduction in blood loss when compared to atenolol [148].

We assessed the blood loss at the end of surgery in both the groups. The mean blood loss in the clonidine group was 411.53(89.33) ml and the mean blood loss in the dexmedetomidine group was 367.37(114.28) ml. This difference was not statistically significant. From our study we found that both the drugs are effective in reducing the blood loss. Since we did not have a placebo group to compare the percentage reduction in blood loss in patients who received alpha 2 agonists like dexmedetomidine and clonidine.

In our study we have noted that the incidence of bradycardia and hypotension was more in dexmedetomidine group. Unfortunately, we did not standardize the fluid administration also we did not analyse the amount of fluids given between the two groups. This could have been an important cause for intraoperative hypotension. Also we are not sure whether clonidine 200 µg is equivalent dose for dexmedetomidine (1µg/kg bolus and 0.5µg/kg/hr).

Limitations

Limitations

1) Due to time constraint and unforeseen circumstances (The BIS monitor malfunction), we were not able to finish the study with the required sample size. We are planning to continue the study till the required sample size at a later date and reanalyze the result.

2) Since the attending anesthesiologist who anesthetized the patient was not blinded about the study drug, it could have caused some bias while treating the patients.

3) We did not have a placebo arm to which we could compare the findings of the other two arms.

4) We did not make a mention of the amount of fluids ie crystalloids, colloids, blood etc administered to the patients, which will have an effect on haemodynamics.

5) We are not sure whether the dose of clonidine and the dose dexmedetomidine used in the study were equivalent.

6) We did not mention the number of patients who had medical co-morbidities in each group which can affect the haemodynamic status after proning.

CONCLUSION

Conclusion

Both, Clonidine and dexmedetomidine decreases the sevoflurane requirement. But dexmedetomidine has better anesthetic sparing property when compared to clonidine. Intraoperative requirement of propofol and fentanyl were same with both clonidine and dexmedetomidine. Recovery time was comparable between the two groups. Both, clonidine and dexmedetomidine are effective in controlling haemodynamics including the blood pressure and heart rate. Both, clonidine and dexmedetomidine are equally effective in reducing the blood loss.

ANNEXURES

CONSENT FORM

This consent form is for patients undergoing spine surgery in CMC, Vellore who have been invited to participate in the study on the effectiveness of dexmeditomidine versus clonidine in reducing anaesthetic requirements in spine surgery.

Name of Principal Investigator: Dr. George Prashanth Kurian

Name of Organization: CMC Hospital Vellore

Name of Sponsor: Fluid research fund and Cardiology Department CMC

Name of Proposal: Evaluation of dexmeditomidine versus clonidine in reducing anaesthetic requirements in spine surgery.

This Informed Consent Form has two parts:

Information Sheet (to share information about the research with you)

Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

I am Dr George Prashanth Kurian, currently doing my post graduate studies in anaesthesiology in CMC, Vellore. We are currently doing a study to compare the effectiveness of dexmeditomidine versus clonidine in reducing the anaesthetic requirements in spine surgery. I am going to provide you with information and invite you to be a part of this study.

There maybe some words that you do not understand. Please stop me and ask as we go through the information. If you have any questions please feel free to ask.

Purpose of the research

Major spine surgery is associated with significant pain during surgery, which can cause significant increase in blood pressure and heart rate which can increase the bleeding risk for which we need to increase the anesthesia drug concentration which further delay the wake up time from anesthesia. There are lot of techniques used to reduce the high blood pressure and heart rate associated with surgery.

One of these technique is using the drugs which are called as Alpha 2-adrenoceptor agonist. This technique helps the surgeon to perform the surgery faster because of the blood less field by reducing the blood loss and operative time, also decreases the anesthetic drug concentration intern helps for faster recovery. Also these drugs produces pain relief effect there by provides improved pain relief effect. Among this group, two drugs are commonly used (Clonidine, Dexmedetomidine) in anesthesia for producing sleep, for pain relief, to reduce the anxiety also to reduce the anesthetic and analgesic drug needed for surgery. Clonidine is a drug which has been in anesthesia for long time. In our hospital we are giving this drug very often for the above mentioned effects. But the Dexmedetomidine is recently introduced in clinical practice and getting very popular in anesthesia because of its strong effects. By giving these drugs we want to see how much the anesthetic drug can be reduced there by how fast they can come out of anesthesia. We want to compare the two drugs and see is there any advantage over one another in terms of anesthesia recovery. If this study proves that one drug is better than the other in terms of waking up from anesthesia, we will likely to follow the technique for the future spine surgery cases.

Type of Research Intervention and Description of Process

We are conducting a double blinded randomized control trial on the efficacy of oral clonidine versus dexmeditomidine as an iv infusion in spine surgeries in reducing the anaesthetic requirements of commonly used anaesthetic drugs.

Eligible patients undergoing two or more level of spinal decompression and instrumented fusion under G. A. with sevoflurane will be randomly assigned to receive either 200 µg of tablet clonidine as premedication followed by saline infusion in a predetermined volume during surgery. (Group C) or injection Dexmedetomidine 1µg/kg bolus over 10 min before induction followed by an infusion of 0.5 µg/kg/hr during surgery till the start of skin closure (Group D). Standard anaesthesia protocols for induction and maintenance will be followed for all.

Sevoflurane concentration will be titrated to keep the BIS between 40-60. Any hypertensive response will be treated with bolus dose of propofol (0.5 mg/kg). If there is no response, fentanyl (0.5µg/kg) will be given. Intra operative hypotension is treated with either ephedrine (5-10 mg bolus) or phenylephrine (50- 100 µg) bolus. Intra-operative heart rate, blood pressure change during the bolus study drug infusion, during intubation and skin incision will be noted. Intraoperatively, after positioning the patient to prone position, the heart rate and blood pressure will be noted every 15 min till the skin closure. Apart from haemodynamic monitoring, end tidal Sevoflurane concentration and MAC of Sevoflurane also will be noted during intubation, skin incision, at prone position, every 15 min after prone position till the end of skin closure. Total dose of fentanyl, propofol used, time of stopping the study drug and sevoflurane, time taken for emergence from anaesthesia will be noted. Episodes of intraoperative hypotension and bradycardia needing treatment will be noted.

Participant selection

Adult patients whose age is > 18 yrs and less than 60 yrs, scheduled for elective major spine surgery. Also we will only be enrolling patients who either have no diseases at all and also patients who have diseases like diabetes mellitus or hypertension in whom the diseases does not affect their functional capacity(in terms of being able to carry out both daily activities and strenuous activity) at all.

Voluntary Participation

Participation in this study is entirely voluntary. If you do not wish to participate you may still avail of all other facilities in this institution will be treated according to current medical treatment guidelines

Duration

This study will run over period of two years.

Side Effects and Risks

Side effects are largely limited to episodes of hypotension and bradycardia which are commonly encountered in the perioperative period and easily managed.

Benefits

You will be receiving a more balanced anaesthetic plan for your surgery which will confer benefits like better haemodynamic stability, less blood loss, less need for a blood transfusion, and less exposure to the effects of volatile anaesthetic agents.

You will also enable the scientific community to better understand the effedtiveness of these useful drugs and and help us to better plan your anaesthesia.

Re-imbursements:

Although the intervention is done free of cost, there will be no monetary benefits for enrolling in this study

Confidentiality

The personal information we collect from this research will be kept confidential. We will not be sharing the identity (name and hospital number) of those participating in the research.. The results of the study will be shared with others in the scientific community through research papers and medical journals.

Right to Refuse or Withdraw

This is a reconfirmation that participation is voluntary and includes the right to withdraw.

Who to Contact

If you have any doubts about this test you may feel free to contact me, Dr George P Kurian, at the department of anaesthesia.

This is my email id: georgekurian14@gmail.com

This proposal has been reviewed and approved by the IRB of CMC Hospital, which is a committee whose task it is to make sure that research participants are protected from harm. It has also been reviewed by the Ethics Review Committee of this hospital

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

a proforma sheet will be maintained detailing his demographics and vitals.

All care will be taken to ensure patient safety.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

Proforma

Comparing the efficacy of oral Clonidine premedication with Dexmedetomidine infusion during the perioperative period - on sevoflurane requirement and recovery from anaesthesia in patients undergoing major spine surgery.

Pre operative period:

Data collected by: Name: Signature
Date:

Section 1 : Eligibility screening

Section 1a: Inclusion Criteria (circle Y/N as appropriate)

Spine surgery involving more than two level Y/N

Age > 18 yrs
Y/N

ASA physical status 1-11
Y/N

Informed Consent provided
Y/N

If the answer is NO to 1 or more questions , then exclude from further data collection. If answer is YES to all then complete section 1b.

Section 1b: Exclusion Criteria:

Age > 60 yrs.
Y/N

ASA 111- 1V Y/N

Patients with creatinine more than 1.5 mg% Y/N

Patients with liver dysfunction. Y/N

Patients undergoing discectomy and single level spine decompression . Y/N

Patient undergoing scoliosis correction
Y/N

Patients on Beta blocker whose HR <50/min (Baseline) Y/N

Pregnant woman
Y/N

Allergy to study drug
Y/N

If the answer is yes to 1 or more questions , then exclude from further data collection.

Section 2 : Data Collection (Preoperative period): Case No:

Hospital No: _____ Age : _____ Sex: M/F ASA – I/II/III/IV

Height : _____ (cm) Weight : --------- (kg) BMI:_____

Diagnosis:
_____
__

Operation:_____
_____

Preoperative assessment: (if any co morbidities: mention here)

CVS :
_____
_____

RS:_____
_____

GI:_____
_____

Renal/Liver/
Endocrine:_____

CNS: (deficits,if any) :
_____

Medication:

H/O intake of opioids/ NSAID/ Antipsychotics/ antidepressant Y/N

Pre op Medication list if any:

Allergies **Y/N**

Data Sheet: Intraoperative Data: Case No:

Hospital No:Age : Sex : M/F

Study Drug **bolus** starting time: **Bolus** End time:

Time	HR/min	BP(Syst./diast/mean	Spo2	BIS	MAC	Et Sevo
Baseline(at the start time)						
5 min						
10 min						
Intubation						

Dose of Propofol given for intubation: (mg) Dose of fentanyl for Intubation: (µg)

Study drug **Infusion** Start time: Study drug **infusion** End time:

Time of stopping the Sevoflurane : Time of Extubation :

Time taken for recovery (stopping of SEVO to time of extubation):

Duration of surgery (Skin incision to closure):

Total Propofolused during maintenance phase: (mg)

Total Fentanyl used during maintenance phase: (µg)

Haemodynamic variables during the maintenance phase

Time	HR/min	BP(Syst./diast/mean	End tidal	MAC	BIS
After prone position (immediately)					
5 min after proning					
10 min					
15 min					
30 min					
45 min					
1 hr					
1hr 15 min					
1 hr 30 min					
1 hr 45 min					
2 hr					

2 hr 15 min					
2 hr 30 min					
2 hr 45 min					
3 hr					
3 hr 15 min					
3 hr 30 min					

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